VOLUME 59 NUMBER 1

ARCHIVES
OF
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JANUARY 1949

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $10.00

Entered as Second Class Matter Oct. 30, 1917, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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Archives of Dermatology and Syphilology

VOLUME 59 JANUARY 1949 NUMBER 1

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PREVENTION OF SYPHILIS

Penicillin Calcium in Oil and White Wax, U. S. P., Bismuth Ethylcamphorate and Oxophenarsine Hydrochloride in Treatment, During Incubation Stage, of Persons Exposed to Syphilis

LEE J. ALEXANDER, M.D.
AND
ARTHUR G. SCHOCH, M.D.
DALLAS, TEXAS

TWENTY months before the time of this report, in November 1946, we began to treat persons known to have been in contact with patients who had infectious syphilis in an attempt (1) to prevent the development of the disease in these persons, (2) to reduce the spread of the disease to others and (3) to reduce the incidence of reinfection. (The persons treated after exposure were clinically and serologically negative when first examined.)

For several years prior to the beginning of this study (since the advent of penicillin therapy) we had practiced and advocated the treating of persons who had had repeated contact (marital and/or otherwise) with patients known to be syphilitic simultaneously with and in exactly the same manner as the infected partners. With this method, the results were excellent; however, we felt that the impracticality and expense of the method prevented its routine use. Therefore, we directed our efforts toward a simpler and more practical approach.

For the routine management of these "uninfected" persons who had been exposed to syphilis we realized that the method must be simple, inexpensive, safe and effective. We felt therefore, that the one visit treatment should be ideal. We knew that in order to prevent the

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The penicillin calcium in oil and wax U. S. P. used in this study was furnished by the Abbott Laboratories.

From the Dallas Syphilis and Venereal Disease Clinic, Parkland Hospital, and the Department of Dermatology and Syphilology, Southwestern Medical College.

Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

This investigation was supported in part by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service.

development of clinical syphilis in these "uninfected" persons we had to direct treatment toward the cure of subclinical syphilis of variable duration. We felt, therefore, that a one day method of treatment might be devisable, since the disease in these cases would be in its earliest form, the incubation stage. Consequently, we decided to use a combination of the known antispirochetal agents, namely, penicillin, an oil-soluble bismuth compound and oxophenarsine hydrochloride, in order to gain whatever synergistic or additive effect these preparations might have. This method of therapy we have designated as "abortive treatment of syphilis."

PLAN OF STUDY

Only persons who had had recent exposure to dark-field-positive primary or secondary syphilis and who were found to be clinically and serologically negative were included in the study. Confirmation of the exposure was ascertained by cross interrogation of the source patient and of the person suspected. Persons who were exposed to primary or secondary syphilis two and three months respectively prior to the interview were not treated.

TABLE 1.—*Results of Abortive Treatment of "Uninfected" Persons in Contact with Patients with Infectious Syphilis*

	Original Treatment	Periods of Observation, Months											
		1	2	3	4	5	6	7	8	9	10	11	12-18
Patients	148	139	133	127	116	111	102	91	86	79	63	52	48
Patients reinfected	...	...	1	...	3	...	...	..	..	..	..	1	1

The exposed persons were formed as impartially as possible into two groups. One group was treated with the abortive method; the other was kept under observation as an untreated (control) group.

Each person in the treated group received an injection of 900,000 units of penicillin calcium in oil and white wax U. S. P. in one buttock, one of 3 cc. of bismuth ethylcamphorate in oil in the other buttock and one of 0.05 to 0.06 Gm. of oxophenarsine hydrochloride intravenously. This procedure requires approximately five minutes in the treatment room.

Each treated person was instructed to return for physical and serologic examinations one week after receiving the abortive treatment and once a month thereafter. As has been the custom with us and with others for years, persons in the control group were followed less stringently with periodic follow-up examinations.

Retreatment with the abortive method was carried out on patients in whom clinical early syphilis developed and in those who were reexposed.

RESULTS OF STUDY

One hundred and forty-eight persons exposed to syphilis were given the abortive treatment. The results of the follow-up observations made each month are shown in table 1. Clinical early syphilis developed in 6

of these patients: in 1 two months, in 3 four months, in 1 eleven months and in 1 fourteen months after treatment.

Data on the 6 patients in whom infectious syphilis developed after they had received abortive treatment are given in table 2. All 6 patients were probably reinfected, 3 with certainty. Two were unable to identify their sources of infection, other than as "pick-ups." One refused to cooperate with us; but eleven months after abortive treatment this patient was treated by us for gonorrhea with penicillin, and three months later (fourteen months after abortive treatment) secondary syphilis

TABLE 2.—*Data on Patients in Whom Infectious Syphilis Developed After Abortive Treatment*

Patient and Date of Abortive Treatment	Diagnosis of Reinfection and Date	Epidemiology		Serologic Findings After Retreatment
		Sources of Infection	Type of Syphilis; Reaction and Date	
E. L. D. 12/16/46	Negative primary, 11/20/47	2 known	Secondary, 11/26/47; other undetermined	Negative, 1 mo.
De. H. 3/4/47	Positive primary, 5/27/47	1 pick-up; 2 known	Unknown; 2 negative reactions	Negative, 11 mo.
F. M. M. 4/11/47	Positive primary, 8/14/47	1 known	Secondary, 8/14/47	Negative, 5 mo.
S. E. 4/8/47	Positive primary, 8/26/47	1 pick-up	Unknown	Negative, 8 mo.
L. B. 11/20/46	Secondary, 1/20/48	Unknown	Unknown; gonorrhea 10/47; seronegative	Pending; cooperation poor; titer 128, reduced to 8 (patient had had gonorrhea in 10/47, but was then seronegative)
E. A. 3/17/47	Seropositive primary, 7/22/47	3 known	Seropositive primary, 8/20/47; negative; secondary, 8/25/47 (this third person contacted had been exposed to secondary syphilis on 6/11/47)	Negative, 9 mo.

developed. The evidence available in these 6 cases, though not conclusive in all instances, supports the idea of reinfection rather than failure of abortive treatment. All 6 patients were retreated by the abortive method. Five responded satisfactorily; the results in the other case are pending at the time of this report.

An additional 6 persons who had been exposed to syphilis and who received abortive treatment were reexposed to infectious syphilis and were reatreated. All were protected a second time against clinical syphilis. These 6 patients have been followed for four to ten months after their second exposure, and all are free of clinical syphilis at the time of writing.

Table 3 shows the outcome for the control group. The group was composed of 161 "uninfected" persons exposed to syphilis who were

not given abortive treatment. One hundred (62.1 per cent) acquired infectious syphilis in the usual course of time. Sixty-one (37.9 per cent) remained serologically and clinically negative, or did not acquire syphilis.

The control group was analyzed further to see whether the incidence of syphilis which resulted from exposure to dark-field-positive primary syphilis differed from the incidence which resulted from exposure to dark-field-positive secondary syphilis. Table 4 shows these results. There was no significant difference; approximately 62 per cent of the persons exposed to either primary or secondary syphilis became infected.

Of the patients who returned one week after receiving abortive treatment, 16.4 per cent showed a provocative effect, that is, a change in the

TABLE 3.—*Incidence of Infectious Syphilis in Control Group*

	Negative and Remained Negative	Negative and Became Positive	Total
Number of persons exposed.....	61	100	161
Percentage	37.9	62.1	100

TABLE 4.—*Incidence of Syphilis in Control Group After Exposure to Primary or Secondary Syphilis*

	Persons Exposed to Primary Syphilis		Persons Exposed to Secondary Syphilis		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Acquired syphilis.....	32	62.7	68	61.8	100	62.1
Did not acquire syphilis	19	37.3	42	38.2	61	37.9
Total.....	51	100	110	100	161	100

serologic reactions from negative at the time of the abortive treatment to doubtful or positive a few days later. Either these persons were on the verge of having clinical syphilis, or the primary lesions were overlooked. All became seronegative by the time of the next observation and have remained so six months or longer.

SUMMARY

This study deals with 309 persons who had been in contact with patients with dark-field-positive primary or secondary syphilis and who were found to be clinically and serologically negative.

One hundred and forty-eight persons in contact with syphilitic persons were given abortive treatment, which consisted in administration of 900,000 units of penicillin calcium in oil and white wax U. S. P., 3 cc. of bismuth ethylcamphorate in oil and 0.05 to 0.06 Gm. of oxophenarsine hydrochloride given at one visit to the clinic.

In 6 of these persons early syphilis later developed, but 3 had definite reinfections and the other 3 were probably reinfected.

Of 161 persons who had been in contact with syphilitic persons and who had not been given the abortive treatment (control group) early syphilis developed in 100, or 62.1 per cent.

Six persons who were exposed to infectious syphilis a second time and retreated were again protected.

In the persons forming the control group the incidence of syphilis after exposure to primary syphilis was the same as that following exposure to secondary syphilis.

Of the persons exposed to syphilis who returned within one week after receiving abortive treatment, 16.4 per cent showed a provocative effect.

CONCLUSIONS

Almost two thirds of normal persons exposed to infectious early syphilis acquire early syphilis if untreated.

Abortive treatment, as described, administered during the incubation stage affords almost 100 per cent protection.

Standard management of patients in contact with syphilis (repeated observations and examinations without treatment) is outmoded.

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ABSTRACT OF DISCUSSION

DR. J. R. HELLER, Washington, D. C.: The procedure described by Drs. Alexander and Schoch tends to disturb the traditional conservative desire to withhold any treatment of syphilis before diagnosis. One might well call this procedure "early preventive treatment" rather than abortive treatment. From the standpoint of public health, it is apparent that treatment during presumed incubation of syphilis offers an economical and efficient tool for control of the disease. The injection of penicillin in the dosage used is well beyond the limits mentioned by Harold J. Magnuson and Harry Eagle (Retardation and Suppression of Experimental Early Syphilis by Small Doses of Penicillin Comparable to Those Used in Treatment of Gonorrhea, *Am. J. Syph., Gonor. & Ven. Dis.* **29**:587-596 [Nov.] 1945). Additional data by Eagle and others indicated that the size of an abortive dose of penicillin varies with the number of organisms in the host and that comparatively small doses of penicillin (100,000 to 300,000 units) might effectively abort syphilis if administered one to four days after exposure. A study to be published is under way by workers of the Department of Health of the City of Chicago and of the public health service, Johns Hopkins Laboratory of Experimental Therapeutics. Persons who have had sexual contact with persons with infectious syphilis are being treated with 600,000 units of penicillin calcium in oil and white wax as soon as they can be located. At the time of this report, 77 persons have received such injections and 69 similarly exposed persons form an untreated control group. Syphilis has developed in 3 treated persons and in 11 persons in the control group. This evidence supports the data reported by Drs. Alexander and Schoch. In my experience, I have not observed so high a percentage of infections due to contact with persons with primary and secondary syphilis as have the authors. Do the persons included in the study represent all possible persons exposed during the

infectious period? I wonder, also, whether Drs. Alexander and Schoch recommend their procedure for all contacts irrespective of social and economic status? The psychic trauma and possible syphilophobia, as well as certain medicolegal complications, have to be considered.

DR. LOREN W. SHAFFER, Detroit: The excellent paper of Drs. Alexander and Schoch should provoke much discussion. They are the first to use penicillin in the abortive treatment of syphilis in persons exposed to infection. Like Mahoney in introducing penicillin in the treatment of syphilis, the authors have seemingly hit on an effective abortive dose from the start. The value of arsenicals in such prophylactic treatment was previously recognized but never adequately evaluated. It was recommended only after very recent exposures. The authors place no limitation of time on the interval after exposure in the use of their abortive treatment, demanding only that patients be seronegative and that clinical evidence of syphilis be absent. In fact, the treatment was used in 6 cases (5 of primary and 1 of secondary syphilis) classified as questionable failures, and in 16 per cent of patients exposed to persons with infectious syphilis the incubation period was so far advanced that the treatment provoked a positive serologic reaction. These persons probably had a symptomless infection. The facts would indicate that the proposed schedule is an effective treatment for early primary syphilis as well as for the abortive cure of syphilis. Dr. Alexander and Dr. Schoch are now in the process of evaluating the schedule treatment of primary and secondary syphilis.

One day treatment methods have been tried by others, including workers at the Chicago Intensive Treatment Center, and have been disappointing even after the administration of huge doses of penicillin intravenously. The effectiveness of the Alexander-Schoch schedule over that of the use of penicillin alone may lie in the combined synergistic action of arsenic, bismuth and penicillin. In the earlier days of intensive arsenotherapy it was found that results were remarkably improved with the addition of a bismuth compound.

Questions arise whether such abortive treatment should not be restricted to cases of a limited time since exposure, and whether a less intensive schedule should not be employed in cases in which only a short time has elapsed since exposure.

The problem of masking syphilis in its incubation period with penicillin treatment of gonorrhea is a serious one. The use of treatment for gonorrhea sufficient to abort incubating syphilis would be indicated if it could be shown to be quite safe and effective. Dr. Alexander's schedule would probably be too intensive for such routine use. Further investigations, however, should be made along this line.

Sixty-two per cent is a higher incidence of infection in persons exposed to early syphilis than is usually observed, as has been indicated by Dr. Heller; but, even if the chances of infection are two out of three it might be argued that for the operative clinic or private patient a "wait and see" policy would be more desirable, since treated persons should be classified as syphilitic and followed up for years, if not for a lifetime. If syphilis develops, the probability of cure in such follow-up cases should be nearly 100 per cent. Of course, contact would be lost in many instances and Schoch's "ping pong" syphilis would remain a serious problem.

Finally, there arises the question of tolerance to 3 cc. of penicillin calcium in oil and white wax, 3 cc. of bismuth ethyl camphorate and 50 to 60 mg. of oxophenarsine hydrochloride given in a single treatment. Evidently tolerance has been satisfactory; time has not permitted its discussion. Crystalline procaine penicillin G in oil would probably be better tolerated, and possibly even more effective than penicillin calcium in oil and white wax.

The authors are to be congratulated on their valuable contribution to the control of syphilis through preventing its development in exposed persons. The study has

been well controlled. They have attacked the problem in a more aggressive fashion than most of us would have dared to do.

DR. ARTHUR J. VON WERSSOWETZ, Chattanooga, Tenn.: The question of systemic prophylaxis of syphilis, or the so-called abortive treatment, is by no means new. Schemes and schedules have been tried throughout the years by various syphilologists, using all the drugs in the armamentarium for treatment of this disease. The results and claims of such procedures usually remained unshaken only in the eyes of their proponents; otherwise, it is still the general consensus among most syphilologists that treatment for syphilis should not be given until a definite diagnosis of the presence of the disease can be made.

To consider the routine acceptance of abortive treatment of syphilis in persons exposed to early lesions, one must establish certain postulates which would justify the procedure. In my opinion the most important are: (1) What is the incidence of infection in persons exposed to early syphilis? (2) Is this incidence sufficiently high to justify the routine abortive treatment of all contacts, without waiting for the development of clinical or serologic signs of the disease? (3) Would such a procedure, as a routine, be sound medically? (4) Could it be adopted as a public health measure? (5) In that sense, would it be worth while economically? (6) Would it result in a decrease in the incidence of syphilis? (7) Can it be justified and upheld legally, if adopted as a routine?

There have been few studies on the actual incidence of syphilis among persons exposed to early syphilis. Data have been compiled on this aspect of the control of syphilis at the Chattanooga Venereal Disease Clinic. The results of five years of study of about 10,000 exposed persons have recently been published (von Werssowetz, A. J.: *J. Ven Dis. Inform.* **29**:132-137 [May] 1948). Only about 50 per cent of persons exposed to primary or secondary syphilis were infected: to be specific, in the marital group only 47.7 per cent were infected. However, the data included those for all stages of syphilis: primary, secondary, early latent, late latent and others. Obviously, abortive treatment would have been of no value to any but persons with presumably "incubating" primary or secondary syphilis following exposure; the data follow:

Total no. of exposed persons investigated	1,250
Total no. of exposed persons examined	927
Persons with new primary or secondary cases discovered	15.3%
Persons who had been exposed and were not infected	36.5%
Persons who had been exposed and were already under treatment or had fully established infection	48.3%

It is obvious that abortive treatment in the amounts proposed would have been indicated only, at best, in 15.3 per cent of all exposed persons located.

Medically, abortive treatment appears unsound as a routine. Thousands of persons annually would receive treatment for syphilis, even though they had never had the disease. "Some of the more sexually active members of our species," to quote Dr. Kinsey, would be receiving such treatment weekly or monthly throughout the years, without knowing when it was actually necessary, if at all. What a fruitful field for an epidemic of anxiety neuroses and syphilophobia!

Time does not permit my quoting the results of studies of syphilis in rabbits treated abortively with penicillin, and the analogies they offer in treatment of the disease in the human subject. However, with the amounts proposed, there is a definite possibility of an asymptomatic relapse or suppression of syphilis, especially since abortive treatment in human beings cannot be given immediately after the questionable exposure. If the treatment could be carried out within forty-eight hours at the latest, it might prove its merits.

As the control of venereal diseases is a public health problem, abortive treatment would, of necessity, be within the jurisdiction of the department of public health. Several obstacles are obvious. One would be the cost of treating thousands of noninfected persons annually. Another would be the legality of such a procedure. In order to establish abortive treatment as a routine public health measure, one should be able to enforce it by law. Enforcement would encroach on the constitutional rights of the individual persons; lack of enforcement would allow the measure to fall short of its intended purpose.

Would abortive treatment affect the incidence of syphilis, resulting in a decrease? Like any hypothetic question of such nature, this cannot be satisfactorily answered. However, since the percentage of cases of infection in which the treatment could be applied is very low, one may argue that the procedure would be only like a drop removed from a bucket of water.

As one trained in legal matters, may I make this general statement: One of the necessary elements of the practice of medicine, actually one which by legal definition confers on a person the right to engage in the healing arts, is the act of determining from the symptoms of the patient what disease or infirmity he is afflicted with, before prescribing any treatment to cure him of the condition. This in medical and legal terminology constitutes the diagnosis.

In the abortive treatment of syphilis this cardinal prerequisite cannot be fulfilled, and so the physician is left, possibly even with the patient's consent to treatment, open to a suit for malpractice for treatment of a condition which may have not existed at all. I believe that in the light of these arguments efforts in the control and prevention of syphilis should remain confined to education and "case finding," and should not extend to "case preventing."

DR. H. M. ROBINSON, Baltimore: My experience with the use of penicillin in its various combinations has not been so rosy as we were led to believe by the many investigators working with the problem, especially by those of the United States Public Health Service. I have seen too many relapses after injections, whether water-soluble penicillin, penicillin calcium in oil and white wax or crystalline procaine penicillin G in oil were used. Actually, to my knowedge, most men are now using, for their private patients at least, a combination of penicillin and arsenic and bismuth compounds. To attempt to prevent syphilis by the treatment of all exposed persons seems to me to fall wide of the purpose of treatment. Let us divide such exposed persons into two groups. They either have or they have not syphilis. There is no incubation period at all. Twenty-four hours, or forty-eight at the very most, after contact with a syphilitic person, a person either has or has not syphilis. I am afraid that the treatment, if he is syphilitic, may fail to eradicate the disease completely. I question whether one day of penicillin therapy, one day of bismuth therapy and one injection of arsenic will accomplish complete eradication of syphilis. Certainly if a person is not syphilitic, he does not require treatment.

If the authors have for their purpose the avoidance of frequent examination of persons exposed to syphilis, they have failed, for even if one day treatment were given to the various exposed persons, frequent reexamination would still be necessary in order to be sure that they had not become infected or relapsed.

DR. G. W. BINKLEY, Cleveland: When this contribution is examined from the standpoint of the duration of the infection, the dosage falls logically into line with what is known about the prevention and control of syphilis. Infection can be prevented, first, by mechanical means, such as use of a condom. No chemotherapy is necessary when inoculation has not taken place. A few moments after exposure, soap and water or other detergent is effective; infection has been prevented with

their use. A few hours later it is necessary to use local chemotherapy, for example. the application of mild mercurous chloride U. S. P. and sulfathiazole, drugs which are provided in the prophylactic kits. Passing over the incubation stage, which the authors have discussed, to the treatment of seronegative primary syphilis, we note that a dose of 2,400,000 or more units of penicillin is necessary for cure. The treatment schedule of Dr. Alexander and Dr. Schoch falls between the dosage for chemical prophylaxis and that for the treatment of seronegative primary syphilis. I believe that the time honored employment of chemical prophylaxis to prevent disease also sets a precedent from a medicolegal standpoint for the proposed treatment of the incubation stage.

Dr. Theodore Rosenthal, New York: Drs. Alexander and Schoch should be congratulated for their courage in entering the jousts in such a highly controversial subject. I believe that the value of this project rests on the percentage of infected exposed persons discovered in any group of the population. I should like to ask Dr. Alexander to give us their figures on the number of patients and the number of others who had been exposed to the disease. If, as he indicated, two thirds of his contacts were named by patients with early syphilis, there may be some justification for this procedure. Before I left New York, a patient with early syphilis had named 11 exposed persons. At the time I left, 5 or 6 of these persons had already been located; 1 had secondary syphilis. According to the authors, all these should summarily be called in and treated for syphilis. Such persons, treated in the manner and with the dose described by the authors, must then be carefully observed at intervals in exactly the same way as persons with proved cases of syphilis, to determine whether cure has actually been achieved. In my opinion, this follow-up care should properly be directed toward a periodic check-up of these persons; should any be found infected, modern therapy would quickly effect a cure. Beyond all other considerations, my medical conscience finds it a bit repugnant to treat a patient for a serious disease like syphilis in the absence of a definite diagnosis. A patient with syphilis requires a lifetime of observation on the part of the physician, while he himself has a lifetime of apprehension.

Dr. Dudley C. Smith, Charlottesville, Va.: In the original work that Brumfield and I did on the subject of patients exposed to persons with infectious syphilis (Tracing the Transmission of Syphilis, *J. A. M. A.* **101**:1955-1957 [Dec. 16] 1933), it was observed that over 75 per cent of these patients were eventually infected. If women only are included (and this is, I think, of practical significance), the incidence of infection is higher. This high incidence of infection among persons exposed to others known to have syphilis seems to me to be justification for the program that Drs. Alexander and Schoch have recommended.

At present, with the development of slower-absorbing penicillin, one may use a short, ambulatory treatment schedule, which produces a high rate of cure in those known to have syphilis. For example, an eight day schedule of treatment with penicillin (3,000,000 to 4,000,000 units) will cure 75 to 80 per cent of persons with primary syphilis. With syphilis in the incubation period, the same amount of treatment would undoubtedly produce a higher percentage of cures. With crystalline procaine penicillin G in oil, to which has been added aluminum monostearate, one injection of 4 cc. (1,200,000 units) will give an effective and detectable quantity in the blood for about seven days. This, in my opinion, is enough penicillin alone to effect cure in 90 to 95 per cent of all cases of syphilis in the incubation period. If bismuth and arsenic preparations are added, as Dr. Alexander recommends, cures may be effected in nearly 100 per cent of cases. This method is certainly justified on the basis of public health and the individual patient's welfare.

An occasional nonsyphilitic patient's receiving this relatively nontoxic schedule of therapy is less significant than not diagnosing the condition for and letting them

many other patients and letting them remain untreated. One makes a diagnosis of syphilis and gives treatment frequently in practice to persons who do not have syphilis because the diagnostic criteria are not faultless. This does not seem unforgivable, in view of the beneficial results to the entire group.

More emphasis should be placed on curing all persons with early infectious syphilis than on doing a little harm to a few persons.

DR. SAMUEL J. ZAKON, Chicago: It is a principle of Anglo-Saxon jurisprudence that a man is innocent until proved guilty beyond a shadow of a doubt. In diagnosis, we must also adhere to this principle: No one should receive any treatment for syphilis until a diagnosis of syphilis has been established beyond the shadow of a doubt. Is this effort anything new in the history of syphilis? No. In centuries past, many efforts have been made to introduce so-called abortive cures of syphilis. With the introduction of each new drug, arsphenamine, bismuth and acetarsone, such an effort was made. It will be recalled that acetarsone was originally introduced on the market as a prophylactic against syphilis. Frenchmen were told that they could swallow six tablets of acetarsone and then "paint the town red" with relative safety. All these treatments and all these efforts failed, for one simple reason: They were unscientific approaches to a serious disease.

DR. LEE J. ALEXANDER, Dallas, Texas: Dr. Schoch and I are not certain that 62 per cent of persons exposed to infectious syphilis will acquire the disease. In an attempt to answer this question with a little more positiveness, we analyzed our records for the year prior to the beginning of this study. Data were checked on persons who when first examined after exposure had been clinically and serologically negative and who had been managed with routine periodic follow-up examinations. [Slide] This slide compares the incidence of clinical syphilis in this group (59.9 per cent) and that in the control group of this study (62 per cent). The efficacy of abortive treatment of exposed persons during the incubation stage necessarily depends on the number of persons who are located. This depends on how promptly and efficiently the investigations of exposure are made. The time is limited by the incubation period of syphilis: Persons must be located before syphilis has become evident; otherwise there remains only the group that is destined to escape infection. Each patient with syphilis was at one time uninfected and had the disease only in the incubation period. This is the type of person who needs to be treated during the incubation stage. Perhaps penicillin, bismuth and arsenic are not necessary in this method of management of exposed persons. Two months before the time of this report, we began treating our "uninfected" exposed patients with penicillin calcium in oil and white wax and with bismuth ethyl camphorate only, omitting the oxophenarsine hydrochloride. Thus far, we have had no failures. We are treating, also with this modification, all patients with gonorrhea who had syphilis previously, in order to prevent reinfection in those persons who might have been exposed to syphilis at the time they acquired gonorrhea. To the question of the effectiveness of the abortive treatment of actual syphilis, the following figures will offer a reply: In April 1947 we began treating patients with infectious syphilis (chiefly secondary syphilis) with the same method. About 140 patients were treated during the first twelve months. Follow-up examinations of these patients ranged, at the time of this report, from two to fourteen months. Fourteen of the patients have been treated a second time, 8 for relapse and 6 for reinfection. We are not recommending this method of treatment. We have no syphilophobic patients yet. We do not tell the patients that they have syphilis. They are told that they have been exposed to syphilis, that they have three chances out of five of acquiring the disease and that if they will take the abortive treatment they will most probably escape infection. Few refuse it.

SENSITIVITY TO TUBERCULIN OF PERSONS WITH ACNE

The Importance of Age in Its Interpretation; a Study of 1,136 Students

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AND
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BOSTON

THE RELATION between acne vulgaris and tuberculin sensitivity has received sporadic attention in the medical literature for the past fifteen years. In a review of the literature up to 1943, Loewenthal [1] cited the work of German investigators of the early nineteen thirties as first indicating the problem. He speaks of the observation by Ramel in 1928 of acid-fast bacilli in the closed lesions of 4 patients with acne vulgaris and of the same worker's discovery of ten more such cases in 1930. In each case the laboratory observation was verified by guinea pig inoculation but none of these patients had clinical tuberculosis. He stated also that Griesbach in 1930 reported acne in no less than 30 per cent of 18,000 cases of active tuberculosis.

In 1934, von Kemeri [2] reported a series of 52 patients with acne, all of whom presented roentgenographic evidence of tuberculosis of moderate severity, positive tuberculin reactions and pyogenic foci. Twenty-two of these patients were cured by the removal of their pyogenic foci. The sole treatment for acne received by the remaining 30 consisted of gradually increasing doses of tuberculin. Of the 30, 27 were cured completely (the acne lesions disappeared); 2 patients improved; the remaining patient became worse. Von Kemeri's observations, together with those of Ramel four years earlier, led him to state the belief that acne vulgaris is a mixed acid-fast and pyogenic infection of the skin.

Reporting from New Orleans in 1938, van Studdiford [3] pointed out the resemblance of acne to some of the tuberculomas of the face. In

This study was done with financial assistance from the Charles H. Hood Foundation.

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1. Loewenthal, K.: Sensitivity to Tuberculin in Acne and Other Non-Tuberculous Diseases of the Skin, Arch. Dermat. & Syph. **49**:799 (June) 1943.

2. von Kemeri, D.: Aetiologie und allgemeine Behandlung der Akne vulgaris, Dermat. Wchnshr. **98**:237, 1934.

3. van Studdiford, M. T.: Diagnostic and Therapeutic Use of Tuberculin in Certain Acneform Eruptions, Arch. Dermat. & Syph. **38**:737 (Nov.) 1938.

2 cases bovine tubercle bacilli were isolated from facial lesions. Twenty-one persons with positive reactions to tuberculin were treated with tuberculin injections over a period of two months. Of these, 10 were cured of their acne and 11 were improved.

In their series of 11 patients with acne in 1942, Lichtenstein and Stillians [4] were disappointed in the results, benefiting only 1 patient with tuberculin therapy.

Loewenthal,[1] in an attempt to show a statistical correlation between tuberculin sensitivity and acne vulgaris reported a series of 231 patients with dermatitis in 1943. Of the 231 patients, 102 had acne and 129 with other cutaneous diseases served as controls. The subjects were divided into two broad age groups: (1) from 13 to 25 years and (2) from 26 to 40 years, on the assumption that acne is seldom seen before 13 or after 40 and that it begins to decline after 25. In his younger group Loewenthal reported the proportion of positive tuberculin reactions to be practically the same among those with acne as among the controls. In the older group, there was a "considerably smaller proportion of positive reactions in those with acne than in the controls." He concluded also, ". . . patients with severe acne tended to show negative to weakly positive reactions to tuberculin and that strongly positive reactions were associated with mild acne."

Lynch,[5] in a series of 13,748 University of Minnesota students reported in the ARCHIVES in 1944, found positive Mantoux reactions in 27 per cent of his controls and in only 22 per cent of the students with acne—a statistically significant difference in such a large group. His series was divided into groups: 1936-1937, 1938-1940 and 1941-1942. He reported, ". . . statistical analysis demonstrates that the difference is great enough to be of significance for each series and for each sex, though the difference is considerably greater in the males," and, speaking of Loewenthal's work, concluded, ". . . both his observations and mine suggest that there is lessened sensitivity to tuberculin in persons with acne."

The purpose of this paper is to present fresh data on a carefully controlled series of 1,136 first year medical and dental students with observations similar to those of Lynch [5]; an attempt will be made to show that the inverse relationship between acne vulgaris and tuberculin sensitivity may be largely due to the statistical error of inadequate age control.

One thousand, one hundred and thirty-six students entering Tufts College Medical and Dental Schools from 1943 to 1947 were tested with

4. Lichtenstein, M. R., and Stillians, A. W.: Tuberculin Treatment of Acne Vulgaris in Tuberculous Patients, Arch. Dermat. & Syph. **45**:956 (May) 1942.

5. Lynch, F. W.: Lessened Sensitivity to Tuberculin in Acne, Arch. Dermat. & Syph. **49**:174 (March) 1944.

0.01 mg. of tuberculin (0.1 cc. of 1 : 10,000 dilution) intradermally. Four hundred and thirty-eight, or 37.7 per cent of this series, had positive reactions to tuberculin. One hundred and forty-six, or 12.8 per cent of the series, had acne. Dividing the group into those with acne and those without (controls), we found positive tuberculin reactions in 33.6 per cent of those with acne and in 38.3 per cent of those without acne. Though the difference of 4.7 per cent is not significant for this series of 1,136, it is of the same magnitude as the significant difference reported by Lynch in his larger series.

When the study is carried a step further, however, and the student group is analyzed by age, two things appear. First, the students with acne tend to be younger than the students without acne, and, secondly, the students with positive tuberculin reactions tend to be older than those with negative reactions. The mean age (or average age) of the

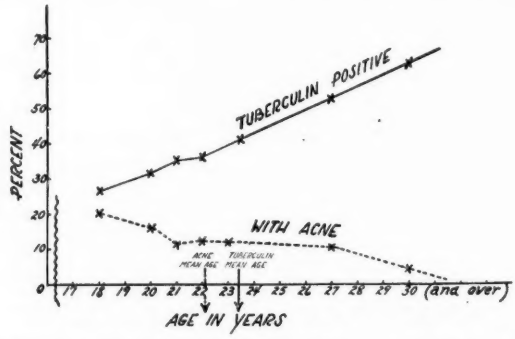
TABLE 1.—*Percentages of Students with Positive Reactions to Tuberculin and Percentages of Students with Acne at Specified Ages*

Age	Total	Students with Positive Reactions to Tuberculin, Percentage	Students with Acne, Percentage
17-19	112	26.8	20.5
20	202	30.7	16.3
21	248	34.7	11.3
22	177	35.3	11.9
23-24	189	40.7	11.6
25-29	176	51.7	10.2
30+	32	62.5	3.1
Total	1,136	37.7	12.8

students with acne was 22.1 years, while the mean age of the students without acne was 22.9 years. The difference in mean age between these two age groups was 0.8 years—a significant difference, the standard error of the difference (sigma) being plus or minus 0.25 years. Age analysis of the entire series shows rapidly increasing proportions with tuberculin sensitivity and decreasing proportions with acne, as age advances (see table 1 and the figure 1). Though, because of small numbers, the acne curve is somewhat irregular in so fine an age breakdown, acne vulgaris and tuberculin sensitivity vary inversely with age, and any attempt to study the relations between the two must be carefully controlled for age.

Applying the principle of age control to our study, the series is subdivided into the smallest possible age groups consistent with stable rates. Relatively stable tuberculin sensitivity percentages are obtained from the large nonacne series. If these age-specific rates are applied to the smaller totals of students with acne in each corresponding age group, an "expected" number of positive tuberculin reactions will be

derived for comparison with the observed numbers. This is equivalent to giving the acne and control groups the same age basis—that of the acne group. When the observed numbers are compared with the expected figures (last two columns of table 2), it will be seen that they vary above and below the expected figures. Were there an actual inverse relationship between tuberculin sensitivity and acne (indepen-



Graph of percentages of subjects with acne and percentage with positive reactions to 0.01 mg. of tuberculin at stated ages in a total of 1,136 students.

TABLE 2.—*Percentages of Subjects with Positive Reactions to 0.01 Mg. of Tuberculin, by Age in Control Group and Observed and Expected Numbers in Acne Group*

	Subjects Without Acne			Subjects with Acne		
Age	Total	No. with Positive Reactions	Percentage with Positive Reactions	Total	No. with Positive Reactions Observed	No. with Positive Reactions Expected
17-19	89	26	29.21	23	4	6.72
20	169	51	30.18	33	11	9.96
21	220	76	34.55	28	10	9.67
22	156	57	36.54	21	5	7.67
23-24	167	65	38.92	22	12	8.56
25-29	158	84	53.16	18	7	9.56
30+	31	20	64.52	1	0	0.64
Total	990	379	38.3	146	49	52.78 (36.1%)

dent of age), the observed numbers of students sensitive to tuberculin in each age group with acne should be more consistently and significantly lower than the expected number. The forty-nine positive reactors in the acne group of 146 give the proportion of 33.6 per cent previously noted as giving positive tuberculin reactions. The 52.78 expected figure in this same group gives the proportion of 36.1 per cent. The original difference between the acne and nonacne groups is more than halved by proper age control.

Because almost all the students in this study were male, no sex differences could be reported for the group. A second series of 1,034 female college students, entering between 1943 and 1947, was obtained through Dr. Helen Ross of the Simmons College Student Health Service. The mean age was 18 years. Analysis of this second series shows a similar tendency toward a younger age distribution for the 191 students with acne. Unfortunately for our hypothesis, and for the earlier literature, this group with acne shows a significantly higher percentage with positive tuberculin reactions—10.5 per cent, as compared with 5.7 per cent for the controls. This appears to be the first report of such an observation in a large series.

COMMENT

A small age difference between any two groups in early adult life, when the tuberculin rate is rising rather rapidly, can account for increased tuberculin sensitivity proportions in the older of the two groups. Given the data, one might easily commit the statistical error of reporting that students who need to shave frequently are more likely to be tuberculin positive than students who need to shave less frequently, since frequency in shaving (in general) and tuberculin sensitivity both increase with age within a certain age range. Thus, one might erroneously relate tuberculin sensitivity to enlarged prostates, closure of certain epiphyses, the number of dental fillings in one's mouth, carcinoma or a galaxy of conditions influenced by age.

No data are here offered on the occurrence of acid-fast organisms in acne lesions. However, if such organisms are present at all frequently, the tuberculin reaction should be more often positive, not less often. The latter observation would require some further assumption, such as tuberculin desensitization. The observations of the present note offer a less complicated explanation for at least some of the reported decreased tuberculin sensitivity in acne, namely, an age basis.

SUMMARY AND CONCLUSIONS

A review of the literature associating acne vulgaris inversely with tuberculin sensitivity is presented, and an attempt is made at its evaluation. Fresh data, presented on a series of 1,136 first year medical and dental students, suggest that students with acne tend to be younger and, therefore, less often tuberculin positive than students without acne. Studies on acne and tuberculin sensitivity should be carefully controlled as to age. Earlier studies do not appear to have fulfilled this requirement to a sufficient degree.

PRESENT STATUS OF QUINACRINE (ATABRINE) DERMATITIS

Report of Six Cases

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MANY physicians and the majority of laymen apparently believe that a fungus is responsible for almost every disease of the skin acquired by members of the armed forces in a tropical climate. In a similarly uncritical manner, the term "jungle rot" is often associated with a supposed fungous infection of tropical origin. The expression was coined by American soldiers in the Pacific Islands and was used to indicate any severe, refractory disease of the skin that occurred there. In my opinion, such conditions that I saw in the Southwest Pacific area resulted from an intolerance to quinacrine (atabrine). Livingood, former dermatologic consultant to the Surgeon General, has expressed agreement.[1]

What is the present dermatologic condition of the veterans who have had quinacrine dermatitis? This question has been asked repeatedly. The following query was sent by a large manufacturing concern to the Industrial Hygiene Foundation of America: "At the present time, our veterans counseling department is faced with the problem of placing returned veterans who have 'jungle rot.' Most of these veterans complain that heat and regular shop dirt cause this condition to reappear; and, accordingly, they request clean, dry work at normal average room temperatures. Our medical director questions the basis of their complaints and would like to have additional information on the subject before a definite policy is established with regard to the placement of veterans afflicted with this condition. In order that we may have the latest information on this subject, we should appreciate receiving your comments and suggestions."

Since intolerance to quinacrine caused most of the cases in question, this report will deal entirely with a group composed entirely of such cases. The history of the patient as it relates to the original condition of the skin is of paramount importance in arriving at the diagnosis of the earlier disease. For this reason, it is well to review the cutaneous reactions which may result from intolerance to quinacrine. I shall

From the Department of Dermatology, University of Pittsburgh School of Medicine.

1. Livingood, C. S.: Personal communication to the author.

divide these into two groups. The more publicized and unusual in character is the lichenoid type, which has been termed atypical lichen planus, New Guinea lichen planus and tropical lichenoid dermatitis. A second variety, which occurs at least ten times as frequently, is an eczematoid dermatitis. In rare instances both varieties occur in the same patient.

LICHENOID TYPE

Clinical Manifestations.—In the active stage, the characteristic lesions are soft, rounded or elongated, violaceous, scaly papules or nodules. As the disease progresses, the lesions become leathery and verrucous. The ankles and the dorsa of the hands are the most frequently affected sites. Next in order of frequency are the legs, arms, buttocks, eyelids and torso. No part of the surface of the body is immune. Acute exfoliative dermatitis is seen in a small percentage of severe cases. In half the cases there occur lesions of the mucous membrane, in the form of tense, gray-white papules on the lips and similar, but reticulated, papules on the buccal mucosa and on any portion of the tongue. Only in the severer cases are there any discernible sequelae.

Sequelae.—Disturbance of Pigmentation: A light brown pigmentation, which is permanent, takes place after the resolution of the nodules and larger papules.

Atrophy of the Skin: At the sites that are pigmented, a thinning of the skin occurs.

Alopecia: Where the scalp or other hair-bearing areas are severely involved, a complete or partial loss of hair results. This alopecia is permanent where the growth has been severely affected for a long period.

Disturbances in Sweat Glands and Sabaceous Glands: During the active phase of this disease, in the severer cases, there occurs a diminution or complete cessation of the functions of the sweat glands and oil glands. Such alteration is usually temporary; at the time of this report only a few persons have conditions associated with this disturbance.

ECZEMATOID TYPE

Clinical Manifestations.—The second variety, more important in this report, is a bilateral eczematoid dermatitis, which usually begins with the appearance of one or more patches of closely set, deep-seated, miliary vesicles on the sides of the fingers. Occasionally, the original lesion is an erythematous, scaly patch. In relatively few cases, the original lesions occur on the dorsa of the feet or in some other location, rather than on the hands. The opposing surfaces of the thumb and index finger and the interdigital web are affected more than any other site. Next, in order of frequency, are the lateral surfaces of the other fingers, the thenar and hypothenar areas and the flexor surfaces of the

wrists. Less frequently involved are the feet, legs, ears, scalp, suprapubic region and scrotum. The mucous membranes are not affected. The external and internal ears are sometimes affected without any other involvement, or with very little dermatitis, in other regions. The original vesicular patches usually clear when treated with a fungicidal paint or ointment. This clearing may take place as many as four times before the lesions become recalcitrant. Remissions of the early lesions have occurred without treatment. The vesicular patches later become transformed into thickened, erythematous, eczematoid patches. Some cases are mild and present only a few small patches; others are severe, and the eruption is accompanied with much inflammation and edema and is disabling. The most striking feature is the bilateral and almost symmetric distribution of the eruption.

Sequelae.—A recurrent eczematoid dermatitis may occur months or years after the original dermatitis. It may take place at previously affected sites or in new locations. The recurrent eruption is similar in appearance to the original dermatitis. Minute vesicles, which may be many or few, appear on an erythematous base. The main element consists of scaly, erythematous patches, slightly or moderately thickened. The symmetric pattern, commonly present in the original picture, is absent. At times there is a circinate configuration, simulating tinea of the glabrous skin. Once established, the recurrent lesions exhibit little tendency to self clearing, are easily irritated and thus aggravated, and are unusually resistant to treatment. There are patients who, although free of cutaneous lesions, complain that their skin is easily irritated and highly sensitive. They insist that the increased irritability did not exist prior to the quinacrine dermatitis.

REPORT OF CASES

CASE 1.—N. C., aged 26, was in the Philippine Islands in April 1945, when blisters appeared on the sides of three fingers on each hand. There was no previous history of dermatoses. Within two months the eruption became eczematized. In July he was hospitalized, and the eruption cleared. After a recurrence in September, the administration of quinacrine was discontinued. Clearing then took place in one month. The next recurrence came in January 1946. When seen in July 1947, the patient had firm, scaly patches on the sides of the second, third and fourth fingers of the left hand.

CASE 2.—I. M., a 35 year old nurse, first experienced skin trouble in New Guinea in March 1945. Being a member of the staff of the same hospital, I had the opportunity to observe her dermatitis at the onset. The original lesions were vesicular patches on the dorsa of the feet and the scalp. On numerous occasions these lesions cleared and reappeared. In December 1945 additional patches appeared on the right palm and thumb. The use of quinacrine was discontinued, and a slow process of clearing began. In April 1946 at the time of her separation from the service, many quiescent, eczematized patches were present. Two months later she returned to nursing duty, and within one month the lesions on the hands were

vesicular and moist. In July a dermatologist prescribed a fungicidal ointment and roentgen radiation. While she was on this regimen new patches continued to appear, and in September the vesicular, eczematoid patches were so widespread that she had to discontinue her work. On November 12, when I saw the patient for the first time since July 1945, she presented ill defined, slightly erythematous patches on the forehead, cheeks, neck and ears. Both arms were almost completely covered with superficial, scaly, erythematous patches. The left palm was studded with miliary vesicles. All the fingers and the backs of both hands presented scaly, eczematized patches. Similar patches, from the size of a pinhead to that of her palm, were present on the posterior wall of the chest and on the thighs and legs. At a later date, the patient was hospitalized; laboratory study revealed moderate secondary anemia and a reversal of the albumin-globulin ratio (serum albumin 2.75 per cent, serum globulin 5.62 per cent). The patient was benefited most by repeated blood transfusions. When last seen, on Feb. 3, 1948, she was unable to follow her profession without suffering renewed activity of the dermatitis on her hands. Even ordinary soaps and water caused exacerbations.

CASE 3.—G. H., a physician, aged 32, was in the Philippine Islands in July 1945, when a vesicular patch appeared on the inner side of the left thumb. This healed promptly after the application of methylrosaniline chloride U. S. P. (gentian violet). In two weeks, the lesion reappeared and persisted longer. On its next reappearance, the eruption failed to heal; at this time both hands were symmetrically involved. When I saw this patient, four months after the appearance of the original lesion, the entire surface of both hands was covered with a vesicular eczematoid dermatitis. Up to this time, he had taken 0.5 to 0.7 Gm. of quinacrine hydrochloride weekly for about eighteen months. The patient recently wrote that he had experienced many periods of exfoliation and that, even up to the present, his hands became red and irritated and itched when he scrubbed for an operation. At the time of writing, he is studying radiology because it is one of the fields of medical practice that does not require much scrubbing.

CASE 4.—G. G., aged 30, an ex-Marine, was in Guadalcanal in 1943 when a vesicular eruption appeared on the insteps and sides of his feet. He stated that the eruption was moist most of the time. Because of it, he was evacuated to Australia. He had been taking 0.7 Gm. of quinacrine hydrochloride weekly. Small, vesicular patches later appeared on his fingers and hands. His dermatitis cleared and reappeared many times. When I first saw him, in April 1947, he presented sharply circumscribed, vesicular eczematoid patches on the extensor surface of the second finger of his right hand and on the back of the left hand, proximal to the fifth finger. These identical sites had been affected on many previous occasions. His feet were free of any lesions. Prior to his military service, he had had no skin trouble.

CASE 5.—H. P., aged 34, was in New Guinea in May 1945, when he experienced a dermatosis "for the first time in his life." There developed superficial eczematized patches about his eyes and on his ears, neck, arms, torso and legs. He stopped taking quinacrine, and moist dressings of boric acid were used; in about one month his skin was almost clear. A number of mild recurrences of the cutaneous eruption followed. Since August 1945 his skin has remained clear. Recently he wrote: "At the present time, as has been the case since my discharge in December 1945, I find that my skin does not have the same appearance that it used to. It is very tender; it becomes infected easily, and if I am out in the sun for any time a very itchy, reddish rash occurs later. If some metals come in contact with my skin it becomes irritated."

CASE 6.—R. L., aged 46, was treated in New Guinea and evacuated to Australia in April 1944 because of an eczematoid eruption on the scalp, forehead, eyelids, ears, hands, penis, scrotum and feet. He had been taking 0.1 Gm. of quinacrine hydrochloride daily for two months. Although the original rash cleared in about three months, he has had frequent, short relapses. When he became overheated or exposed to the sun, highly pruritic, fine vesicles on an erythematous base appeared on many areas of his body. When seen recently, he had involuting, fine, vesicular, erythematous patches on the chest, abdomen and inner portions of the thighs.

COMMENT

Although the term "jungle rot" was originally used to indicate severe, refractory cutaneous eruptions, veterans have recently been applying the term to minor dermatoses which they allege they picked up in the Pacific. These persons usually have dermatophytosis, which, they will admit, was never incapacitating and did not require hospitalization. Severe dermatophytosis was not a problem in the Southwest Pacific.

One may properly ask how a diagnosis is to be made in a case of the eczematoid type if there is no characteristic picture. The high incidence of this dermatitis led to an investigation of the cause. No fungi were recovered, and no common contactant was present. When the taking of quinacrine was discontinued, improvement was seen in two to four weeks. Army records give convincing proof that eczematoid dermatitis occurred frequently in troops undergoing suppressive quinacrine therapy and rarely in others.

Eczematoid dermatitis is not a common manifestation of reaction to drugs, but arsphenamine, the sulfonamide drugs, chloral hydrate and cinchophen have been known to produce such a reaction. Recurrence of the lesions and involvement of additional regions long after administration of quinacrine has been stopped probably indicate that a specific eczema has become a nonspecific one. This alteration was described by Becker and Obermayer [2]; they stated that such a change is important when therapy is considered because one is unlikely to get a favorable result from specific therapy after nonspecific hypersensitiveness has occurred.

In discussing this part of the problem, Livingood [1] stated:

I have the strong feeling that one of the things which quinacrine did to the skin was to broaden the allergic base. By this I mean that persons became sensitive to contactants, foods and other allergens after they had acquired a cutaneous reaction to quinacrine. In my mind, this explains the persistence of the eruption in some cases after the discontinuation of the drug. As a matter of fact, it is my feeling that literally hundreds of persons now have various types of chronic eczematous eruptions only because they had quinacrine dermatitis during the war, and that some of them will continue to have recurrences despite the fact that they may never

2. Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, ed. 2, Philadelphia, J. B. Lippincott Company, 1947, p. 90.

use quinacrine again. This is not an unusual concept. As a matter of fact, one sees examples of it all the time. A person acquires a contact type, eczematous allergic dermatitis, to a metal ring, for example, and this area of the skin then becomes sensitized to many other contactants, as well as ingestants. I have clearly demonstrated in some of my patients that a person may acquire a food allergy only after the development of a contact type of allergic dermatitis which happens to become eczematous and chronic and does not disappear promptly after removal of the contactant.

There is no practical way of determining the incidence of recurrence in cases of eczematoid dermatitis. Probably in most cases the skin has cleared and has remained clear. In a few the condition has never cleared completely, and in a small percentage of cases it has cleared but the patients are subject to recurrent attacks of eczematoid dermatitis. The percentage of recurrences in cases of quinacrine-produced eczematoid dermatitis appears to be much higher than that in cases of eczematoid dermatitis from other causes.

The frequency with which the original eczematoid dermatitis and the recurrent lesions are treated with fungicidal preparations indicates that a resemblance to tinea is often present. In the original dermatitis the fungicidal preparations seldom cause irritation, but in the late recurrences they cause irritation and extension of the process.

SUMMARY

Veterans have residual lesions and recurrences of eczematoid dermatitis which they acquired in the tropical areas during, or after, the recent war.

In its original form this dermatitis is, at least in part, caused by an intolerance to quinacrine (atabrine). A polysensitization takes place, and the process is continued or made worse by various agents.

Affected persons are increased risks in any occupation requiring exposure to heat, friction or chemicals.

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AN ANALYSIS OF BASAL METABOLIC RATE AND BLOOD CHOLESTEROL DETERMINATIONS

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DERMATOLOGISTS regard the administration of thyroid extract as helpful for many cutaneous conditions. However, the concept of its value in many cases is vague, as evidenced by such textbook statements as "thyroid may be helpful." Our discussion and case reports will attempt to show that it may be possible to evaluate the need for thyroid therapy in chronic dermatoses. We will point out that a high basal metabolic rate in itself is not a contraindication to the administration of thyroid if the blood plasma cholesterol is high. We feel that internists do not commonly appreciate that a basal metabolic rate may be falsely high in a patient with a general dermatosis and that dermatologists do not commonly appreciate the fact that hypercholesteremia may indicate hypothyroidism.

Edelman [1] reported the cure of eczema with thyroid extract; recurrences and remissions were brought on by withdrawing and renewing its administration. Tauber [2] used thyroid and epinephrine in cases of exfoliative dermatitis of practically all types, working the dose up to 2 grains (0.13 Gm.) of thyroid twice a day if tolerated and epinephrine 5 minims (0.31 cc.) twice a day. He did not treat chronic contact dermatitis in this manner and felt that his 2 patients with lymphoblastoma were not helped. He felt that both arsenical exfoliative dermatitis and the so-called idiopathic types of conditions were helped by these drugs.

About fifteen years ago we noted that an occasional patient with exfoliative dermatitis or generalized chronic eczema, despite a high basal metabolic rate, would tolerate the administration of thyroid extract well. It was not uncommon to find a basal metabolic rate of +40 to +60 per cent in an elderly man with idiopathic exfoliative dermatitis.

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, June 5, 1947.

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1. Edelman, M. H.: New York M. J. **107**:450-452, 1918.
2. Tauber, E. B.: Univ. Cincinnati M. Bull. **7**:73-75, 1935.

We found that he not only would tolerate thyroid extract, perhaps 1 grain (0.065 cc.) two or three times daily, but that his eruption gradually improved and his pulse rate declined toward normal from a rapid rate. We were inclined to feel that the patient's high basal metabolic rate was usually due to restlessness plus energy irradiation from an inflamed skin, rather than from thyroid overfunction. We even deduced that actually hypothyroidism was present in spite of a high basal metabolic rate, inasmuch as thyroid extract in considerable dosage was often tolerated well.

We found over a few years, however, that this simple syndrome did not always work out this way. One man of 75 with a chronic exfoliative dermatitis and a basal metabolic rate of +55 per cent was given thyroid extract, 1 grain (0.065 cc.) daily. A thyrotoxic state promptly developed, and he died. There seemed to be no constant relationship between the basal metabolic rate and the dermatitis. In some cases the basal metabolic rate would be high. In other cases with just as severe cutaneous involvement, discomfort and restlessness, the basal metabolic rate would be normal, or nearly so.

Normal basal metabolic rates seemed to occur more generally in cases of chronic contact irritant origin, as in ragweed dermatitis of several years' duration. If the exfoliative dermatitis or chronic eczema proved to be external in origin or to be caused by such drugs as arsenic compounds or coal tar products, or by one of the lymphoblastomas, thyroid extract was not likely to help. On the other hand, in cases without obvious cause for the dermatitis, thyroid extract was often helpful.

During the last five years we have found a study of the blood cholesterol level on patients with exfoliative dermatitis helpful. Cholesterol is an unsaturated aromatic alcohol: the empiric formula is $C_{27}H_{45}OH$. It is not a fat but is concerned with fat absorption and metabolism. Classed with the lipids,[3] it is intimately related to many biochemical substances and reactions. It is one of the precursors of vitamin D.[4] It is the forerunner of the suprarenal cortical secretion and the probable source of the sex hormones.[5] It is one of the three main constituents of the bile and the probable source of the bile acids.[5] The normal level of plasma cholesterol ranges from 120 to 200 mg. per hundred cubic centimeters; 25 to 30 per cent of this is free cholesterol and the rest is combined with fatty acids and esters.[6] Authors

3. Boyd, W.: The Pathology of Internal Diseases, ed. 2, Philadelphia, Lea & Febiger, 1936.

4. Nicholson, D.: Laboratory Medicine, ed. 2, Philadelphia, Lea & Febiger, 1939, pp. 217-218.

5. Lehman, R. G.: Ohio State M. J., **41**:430-431, 1945.

6. Stitt, E. R.; Clough, P. D., and Clough, M. D.: Practical Bacteriology, Hematology, and Animal Parasitology, ed. 9, Philadelphia, The Blakiston Company, 1942, pp. 677-678.

differ as to what should be accepted as the normal fasting plasma cholesterol. Hurxthal and Simpson [7] concluded that the average normal fasting value was 180 mg. per hundred cubic centimeters of blood. They showed that the blood cholesterol was high in hypothyroidism. Escamilla [8] reported a case of myxedema with a fasting blood cholesterol of 953 mg. per hundred cubic centimeters and a basal metabolic rate of —38 per cent. Craig, Lisser and Soley [9] reported 2 cases of spontaneous myxedema; in 1 there was a basal metabolic rate of —38 per cent and a blood cholesterol of 667; in the other there was a basal metabolic rate of —35 per cent and blood cholesterol of 926 mg. per hundred cubic centimeters. These were regarded as unusually high levels.

Assuming a normal level of blood cholesterol to be about 180 mg. per hundred cubic centimeters, we felt safe in regarding cholesterol readings above 200 mg. as indicating likely hypothyroidism, for the level of cholesterol rises as the thyroid function falls. Here, then, was a guiding safety factor worthy of note when considering the administration of thyroid extract. For example, with a basal metabolic rate of +50 per cent and a blood cholesterol level of 280 mg. the basal metabolic rate might be about 50 per cent wrong. A basal metabolic rate of —25 per cent would probably fit a cholesterol level of 280 mg.; in other words, the high basal metabolic rate was misleading and due to restlessness and energy irradiation. Such a patient would be helped by administration of thyroid extract.

We have found it relatively easy to exclude other conditions causing hypercholesteremia from our series. Late in pregnancy the blood cholesterol is frequently elevated.[4] In the nephrotic syndrome the blood cholesterol is increased, but edema, albuminuria and decreased serum albumin are present. In unregulated diabetes mellitus there is often decided lipemia, often with a blood cholesterol level of 350 to 600 mg. per hundred cubic centimeters.[5] Xanthomatosis of both diabetic and nondiabetic varieties usually is associated with hypercholesteremia,[5] as are other lipid dystrophies.

Difficulties arise, of course, from the fact that in an occasional patient the blood cholesterol normal level may be much lower than 180 mg., perhaps caused by a prolonged restricted diet or enzyme and absorptive deficiency. Probably a low cholesterol reading prohibits the administration of thyroid extract in these cases or at least indicates caution and small initial dosage.

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7. Hurxthal, L. M., and Simpson, H. W.: J. Clin. Endocrinol. **1**:450-452, 1941.

8. Escamilla, R.: J. Clin. Endocrinol. **2**:33-35, 1942.

9. Craig, L. S.; Lisser, H., and Soley, M. H.: J. Clin. Endocrinol. **4**:12-16, 1944.

The following case reports illustrate the points we have discussed, i. e., a general dermatosis, such as exfoliative dermatitis or eczema, a high basal metabolic rate from energy irradiation and restlessness, a high level of blood plasma cholesterol and a good therapeutic response to the administration of thyroid extract.

REPORT OF CASES

CASE 1.—Mrs. T. V., aged 64, following some garden work, experienced erythema, edema and coarse scaling of her arms and legs. This became universal in two weeks and did not subside after three months of soothing baths, wet dressings and soothing ointments. She had taken no drugs. Her past history was irrelevant and without allergic tendencies. Results of her general physical examination were essentially normal except for a blood pressure of 190 systolic and 94 diastolic. The lymph nodes were not enlarged. The urine was normal. Fractional gastric analysis showed no free hydrochloric acid until histamine was given at the one hour period; in another half-hour the total acid rose to 32 per cent, with 16 per cent free acid. The blood cell count showed hemoglobin 13.5 Gm. per hundred cubic centimeters, red blood cells 4,460,000, and white blood cells 9,000 with a normal differential count with 9 per cent eosinophils. The red blood cell sedimentation rate was 40 mm. in one hour. Fasting blood sugar was 89 mg. per hundred cubic centimeters, blood cholesterol 340 mg. and basal metabolic rate + 35 per cent.

The soothing therapy which this patient had received elsewhere was continued and thyroid therapy was begun, with the dose gradually increased to 1 grain, (0.065 Gm.) twice a day. This was well tolerated. She also received dilute hydrochloric acid, 2 cc., with each meal. Her skin improved gradually, and she left the hospital in three weeks. Six weeks later her skin was practically normal and her blood cholesterol was 190 mg. per hundred cubic centimeters. Treatment with thyroid extract and dilute hydrochloric acid was continued.

CASE 2.—Mr. B. G., aged 67, presented a pronounced universal exfoliative dermatitis of six weeks' duration. He had taken "electric baths" and used sulfur ointment as "a weight-reducing measure" before the onset of the dermatitis. No drugs had been taken. Results of his general examination were essentially normal with the exception of moderate inguinal adenitis and several badly infected teeth. Results of urinalysis and gastric analysis were normal. The blood cell count showed hemoglobin 13.4 Gm. per hundred cubic centimeters, red blood cells 3,990,000 and white blood cells 10,300, with a normal differential count with 4 per cent eosinophils. Blood nonprotein nitrogen was 44 mg. per hundred cubic centimeters. His basal metabolic rate was + 44 per cent. His blood plasma cholesterol was 342 mg. per hundred cubic centimeters.

During three months in the hospital this patient received soothing baths and ointments, liver extract, iron, multivitamin therapy and thyroid extract, 1 grain (0.065 Gm.) twice a day. His infected teeth were removed. On dismissal, his skin was normal, his blood cholesterol was 198 mg., his blood nonprotein nitrogen 28 mg. and his basal metabolic rate was +4 per cent. He had remained in good condition as of the time of reporting.

CASE 3.—Mrs. H. G., aged 64, presented a generalized patchy eczema of seven years' duration. This was most pronounced on the lower legs, with pigmentation, thickening and scaling. Varices with thrombosis were not the cause of the eczema. This was confirmed by a specialist in vein surgery. Otherwise, general physical examination gave normal results. Numerous allergic studies had

been useless. The urine was normal. Gastric analysis showed no free hydrochloric acid, total acid being 16 per cent at one hour. The blood cell count showed hemoglobin 13.4 Gm., red blood cells 4,310,000 and white blood cells 6,100, with a normal differential count with 6 per cent eosinophils. The basal metabolic rate was + 43 per cent. Blood cholesterol was 287 mg. per hundred cubic centimeters.

The patient was given soothing baths and ointments, dilute hydrochloric acid, 2 cc. three times a day, and thyroid extract, ½ grain (0.033 Gm.) three times a day. She was apparently healed in twenty-two days, when her basal metabolic rate was + 6 per cent and her blood cholesterol 192 mg. per hundred cubic centimeters. Treatment was continued with thyroid extract ½ grain (0.033 Gm.) twice a day.

CASE 4.—Mr. J. M., aged 51 presented severe universal erythema, with pigmentation and exfoliation. He was moderately emaciated and had severe contractures of the knees. The patient had spent ten years in another hospital, most of his waking hours in a potassium permanganate bath in an attempt to control discomfort. The tub was rather short, and we felt that this contributed to the contractures. On his admission, we considered a diagnosis of pemphigus foliaceus, but our final diagnosis was severe exfoliative dermatitis. The urine was normal. Gastric analysis showed no free hydrochloric acid, the highest total amount of acid being 23 per cent in one and a half hours. The blood cell count showed hemoglobin 13.1 Gm. per hundred cubic centimeters, red blood cells 4,500,000 and white blood cells 5,900, with a normal differential count with 2 per cent eosinophils. Blood serum protein was 7.57 Gm. Blood cholesterol was 530 mg. per hundred cubic centimeters. The basal metabolic rate was + 55 per cent.

Soothing baths and ointments were employed, and thyroid extract was increased quickly to 2 grains (0.13 Gm.) twice a day. Dilute hydrochloric acid and multivitamins were administered. The knee contractures were gradually straightened by orthopedic manipulation and splitcast traction. In two weeks the blood cholesterol was 225 mg. per hundred cubic centimeers; in seven weeks it was 191 mg. and the basal metabolic rate was + 4 per cent. The patient left the hospital in good condition on his eighty-third hospital day. He continued treatment with thyroid extract and dilute hydrochloric acid and at the time of reporting was up and about his farm.

CASE 5.—Mrs. A. T., aged 73, presented erythema and coarse epidermal exfoliation of pronounced degree on the extremities and neck and to a lesser extent on the trunk. This had been present for four months, after an attack of the "flu." She had "always" experienced indigestion and belching. Otherwise her history and physical examination added nothing. The urine was normal. Gastric analysis showed no free hydrochloric acid, total acid reaching 10 per cent. The blood cell count showed hemoglobin 13.1 per cent, red blood cells 4,700,000 and white blood cells 5,400, with a normal differential count with 6 per cent eosinophils. Plasma protein was 5.5 mg. per hundred cubic centimeters, basal metabolic rate + 42 per cent and blood cholesterol 297 mg. per hundred cubic centimeters.

Soothing baths and ointments were used locally. Dilute hydrochloric acid, 2 cc., was given three times a day with meals, and thyroid extract, ½ grain (0.033 Gm.) was given three times a day. In three weeks the patient was healed. The basal metabolic rate was then + 3 per cent, blood cholesterol 186 mg. per hundred cubic centimeters and plasma protein 7.1 mg. per hundred cubic centimeters.

COMMENT

It is likely that from time to time more and more cases of chronic eczema and "idiopathic" exfoliative dermatitis will be found due to various endocrine failures, focal infection, avitaminosis or senile atrophy

of various organs. The protein-digestive and blood-protein balance may be another important element in some cases. Four of our 5 patients had achlorhydria. In 3 cases the blood serum protein was not determined; in 1 it was normal, and in 1 it was low but became normal with treatment. Goldsmith [10] showed that patients similar to ours may be helped by giving protein hydrolysates by mouth.

We believe that our observations and results in these cases show that these patients were originally hypothyroid, as evidenced by high levels of blood plasma cholesterol. In spite of a high basal metabolic rate, they were benefited clinically by taking thyroid, and the basal metabolic rate and blood plasma became approximately normal in each case.

CONCLUSION

The administration of thyroid extract is safe and beneficial in patients with general inflammatory dermatoses who exhibit a high basal metabolic rate, if the blood plasma cholesterol is elevated.

ABSTRACT OF DISCUSSION

DR. CHARLES C. DENNIE, Kansas City, Mo.: This paper is thorough, concise and timely. The proposition is plainly stated. Certain elderly persons with chronic dermatoses have a high basal metabolic rate accompanied with high blood pressure and high blood cholesterol. The authors believe that the basal metabolic rate is false and that its high index is due to restlessness, sleeplessness and high skin cell metabolism.

The patient is not in a state of hyperthyroidism, but in one of hypothyroidism. The authors have substantiated their observations by successfully feeding these patients thyroid although the basal metabolic rate was high. Not only did the skin become normal but the basal metabolic rate in each case also returned to normal. The high blood pressure was reduced.

The clinical range of the conditions is very narrow. The authors exclude arsenical dermatitis, idiopathic exfoliative dermatitis, the lymphoblastomas, contact dermatitis and external cutaneous allergies and confine their remarks to chronic eczemas, chronic exfoliative dermatitis and intense itching with edema. Gastric analysis showed low or absent hydrochloric acid. I believe this to be the rule in this type of case.

Hypothyroidism must be considered in all patients with the type of dermatoses described, even though the blood pressure and basal metabolic rate are both above normal. High blood cholesterol content overrides all other observations in making a diagnosis of hypothyroidism.

Myxedema is not always accompanied with hypercholesteremia, and the reverse is true. So many unknown chemical factors exist in the thyroid gland the action of which is unknown that the feeding of this substance is often accompanied with unfavorable manifestations. Young women with low basal metabolic rates and the clinical manifestations of hypothyroidism may not be able to take even the smallest effective dose of thyroid.

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10. Goldsmith, N. R.: Possible Benefit from Protein Hydrolysates for Exfoliative Dermatitis, Arch. Dermat. & Syph. **55**:397 (March) 1947.

It has been my experience that with the type of condition described the patient suffers not only from thyroid disturbance but also from an insufficiency of estrogenic or androgenic substances. The addition of these substances to the therapeutic regimen has been of immense value.

The majority of these diseases occur in the very young or the elderly. There is no doubt that many of these problems could be solved that are not solved by an observation of the combination of points that have been made. Finally, in the handling of these cases, it also should be taken into consideration that many of the women past middle life, who have no cutaneous manifestations, do have hypothyroidism. They have many manifestations pointing to hypothyroidism. They are overweight. They have edema of the legs. Their blood pressure is low. Their basal metabolism is a little low. They are tired all the time. Gastric analysis shows total lack of hydrochloric acid.

With a proper regimen there is loss of edema, the weight is reduced and there is a much better feeling toward life.

Therefore therapeutic measures may be confined to: feeding of thyroid; increase in protein intake, mostly by mouth; decrease of salt in the diet or substitution of potassium salt; reduction of fluid intake, which is important in the patients who have edema or who are overweight, and the use of the sex hormones in conjunction with the feeding of thyroid in most of the cases.

Dr. William Harvey Guy, Pittsburgh: There are three things that interest me particularly: First, the role of hypercholesteremia; second, the interrelationship of the basal metabolic rate with cholesterol determination, and, finally, the influence of thyroid in the treatment of the disease. My interest in cholesterol dates back many years and began primarily at a Central States Dermatological meeting in Cincinnati. Some of you who were there will remember the young medical student who discovered in the course of the physical examination that he had pronounced hypercholesteremia. With reduction in the intake of fats and administration of bile salts, an eruption he had had since infancy cleared and remained clear. I have seen that sort of thing occur often. I think that it is of interest, also, to review the basal metabolic rate with reference to the hypercholesteremia, because of the fact that occasionally—I have seen 2 cases—one sees cases in which the basal metabolic rate is very high, in which one ordinarily would not remotely consider the use of thyroid extract in treatment; the indication for the administration of thyroid is the presence of decided hypercholesteremia in connection with the high basal metabolic rate, indicating it to be a false reading. There follows the paradoxic clinical clearing of a chronic condition when one would not have thought of using thyroid extract. This report is another step toward the elimination of the diagnosis of idiopathic scaling erythroderma.

Dr. Richard L. Sutton Jr., Kansas City, Mo.: I feel that it is possible to administer thyroid accurately and correctly without regard to determinations of basal metabolic rate at all. The person who is normal has a normal supply of thyroid. Any additional thyroid is too much. One may give a small dose to such a person and observe overdose symptoms if one is expert in recognizing them. Not everyone is aware of and identifies the symptoms of minor overdosage, such as morning headache, slight tension, restlessness, inability to get to sleep at night, vertigo and weakness.

If one can give a patient thyroid without evoking symptoms of overdosage, one may assume that the person did not have the thyroid supply he needed and required thyroid; otherwise any more would have been too much. The

ability to arrive at the right dose accurately comes only with considerable experience. Basal temperature is another indication of thyroid want and thyroid dosage. A temperature less than 97.8 F., determined accurately with the thermometer left in the mouth for five minutes before the patient arises from bed in the morning, suggests the possibility that thyroid is desirable. If one has given thyroid and the basal temperature rises and approaches 98.2 F., there will be symptoms of overdosage.

The patient who feels a need for stimulation and drinks much coffee does not tolerate thyroid. When coffee is eliminated from the diet and thyroid is given, the picture becomes clear.

As the overadministration of insulin causes hypoglycemia, so the overadministration of thyroid causes hypolipemia. When the thyroid overdose symptoms are severe, a great amount of fat should be given, with large quantities of milk along with acetylsalicylic acid. Some who tried my thyroid treatment for acne observed such overdosage symptoms and then dismissed the whole plan. They could avoid unpleasantness by giving acetylsalicylic acid and milk fat when they have an overdose of thyroid with which to deal. One must reach the top dose and drop back, staying within the limits of proper dosage. Too much is wrong, and too little will not have the desired effect.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: This paper represents a laudable attempt to rationalize the use of a drug which has been applied empirically for a long time in the treatment of obscure disorders of the skin. The basal metabolic rate is a function of the carbon dioxide-oxygen exchange, and the formula that is used assumes a standard loss of heat from a calculated area of body surface. In exfoliative dermatitis, there is usually an abnormal increase in loss of heat from the surface of the body, and in such cases the basal metabolic rate may be reported as + 50 or 60 per cent, which value must be discounted inasmuch as the standard formula no longer obtains. Secondly, if the level of cholesterol is found to be above normal, it is advisable to repeat the test and to include the measure of the cholesterol esters, phospholipids and the total fatty acids in the blood. One should be cautious in the interpretation of the effects of treatment of dermatologic disorders by the use of thyroid extract.,

DR. FRED D. WEIDMAN, Philadelphia: Whenever there is a discrepancy with laboratory observations, it is well to inquire into the basis for those observations and to check whether the explanation may reside therein. I have thought for a long time that perhaps when one is dealing with a structure such as the skin, the approach to the matter of basal metabolic rate is through the wrong avenue. Dr. Brunsting has introduced that topic.

The original approach to the determination of the energy output of the body was through the determination of the production of heat, and the calorimeter was the instrument originally employed for that purpose. That, of course, is predicated on the radiation of heat from the skin. When one is dealing with a skin that is damaged, a monkey wrench is thrown into the machinery. In widespread dermatoses, it would be a splendid problem for someone to undertake to compare the basal metabolic rate as calculated by the present simpler method involving the measurement of carbon dioxide with the figure obtained by the use of the calorimeter. I realize that the calorimeter is a more cumbersome method and hardly practical for routine work, but from the point of view of investigation, perhaps it would have important applications in respect to cutaneous diseases other than idiopathic exfoliative dermatitis.

DR. CHARLES C. TOMLINSON: Dr. Sutton seems to use thyroid extract rather indiscriminately. With a high basal metabolic rate, it is my belief that a blood cholesterol determination should be made in all cases before administering thyroid. The papers of Dr. Keim, Dr. Guy and this one would seem to indicate that there has been need for improving therapy in chronic more or less generalized eczematous dermatoses. Dr. Keim pointed out the importance of attention to serum protein levels and Dr. Guy the importance of faulty nutrition, with particular emphasis on protein insufficiency. Each of the three papers prepared independently has indicated the frequence of achlorhydria in these cases. I hope that our suggestions of blood cholesterol determinations as an indication for thyroid therapy may prove helpful.

NODULAR NONSUPPURATIVE PANNICULITIS (WEBER-CHRISTIAN DISEASE)

Report of a Case in Which an Infiltrate of Polymorphonuclear Leukocytes Represented the Earliest Lesion

WALTER F. LEVER, M.D.
BOSTON

UP TO THE time of this report, 33 cases of relapsing febrile nodular nonsuppurative panniculitis have been reported.[1] All authors agree that the definitive histologic lesion consists of a granulomatous infiltrate in which foamy macrophages predominate. Little agreement exists, however, about the initial histologic change. Ungar [1] recently described the earliest lesion as an infiltrate composed of polymorphonuclear leukocytes. The present case supports his evidence.

REPORT OF CASE

History.—A 33 year old white man first noted, early in March 1945, a red, tender, subcutaneous nodule in the left inguinal region. Two weeks later two similar nodules developed on the buttocks. By the end of the month all three lesions had disappeared.

From July 1945 to June 1946 the patient had six similar episodes, each characterized by fever (temperature as high as 104 F.) and by the development of red, tender, subcutaneous nodules. The nodules varied in number from three to twelve per episode, and occurred on the shoulders, trunk and extremities. Each attack subsided in two to three weeks, without medication. The longest interval between attacks lasted two months.

On June 30, 1946 the patient was admitted to the Massachusetts General Hospital with a typical attack, which had begun six days previously. He presented three tender, red, subcutaneous nodules, one on the left buttock, measuring 5 by 6 cm., and two on the right thigh, measuring 3 by 5 cm. and 7 by 8 cm. respectively. No areas of scarring or depression were noted. The patient's temperature was 103 F.

Biopsy of a lesion present for fifteen days was performed. Aerobic and anaerobic cultures of the specimen were sterile. Histologic examination revealed the characteristic appearance of relapsing febrile nodular nonsuppurative panniculitis. The patient was asked to return as soon as possible after a new lesion had appeared. On Oct. 8, 1946 he returned for biopsy of a lesion which had been present for less than twenty-four hours.

From the Departments of Dermatology and Pathology, Massachusetts General Hospital.

1. Ungar, H.: Relapsing Febrile Nodular Inflammation of Adipose Tissue (Weber-Christian Syndrome): Report of a Case with Autopsy, J. Path. & Bact. **58**:175, 1946

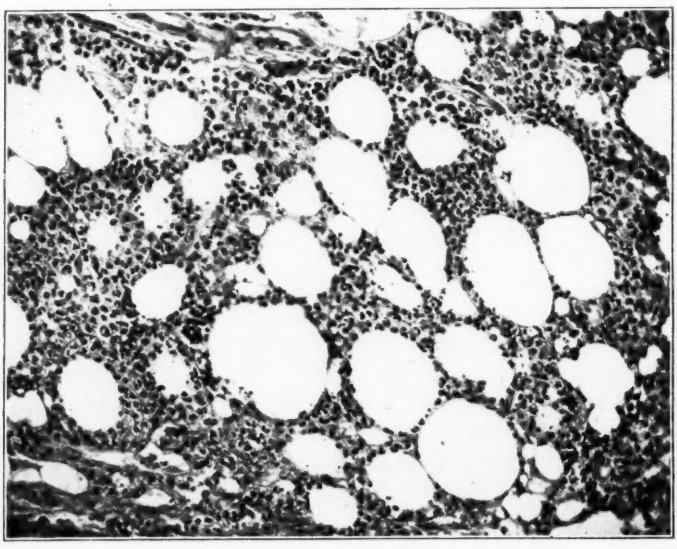

Fig. 1.—Lesion less than twenty-four hours old. The infiltrate is composed predominantly of polymorphonuclear leukocytes. × 200.

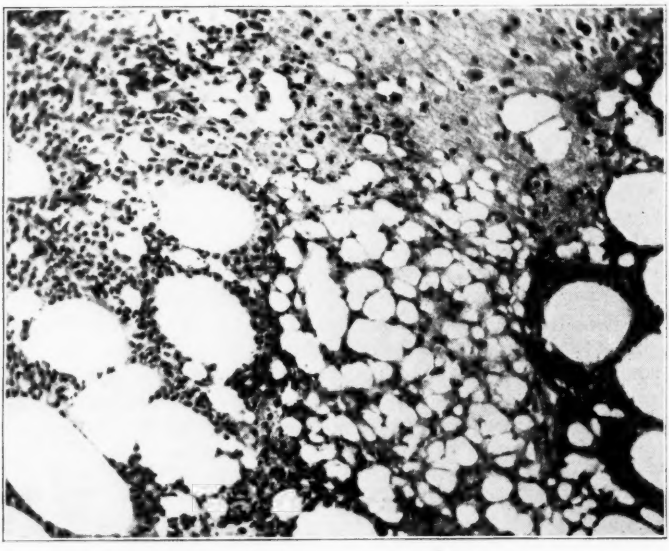

Fig. 2.—Lesion less than twenty-four hours old. The fat cells in the center are undergoing liquefaction necrosis. × 200.

Histopathologic Examination.—The early lesion showed, limited to the subcutaneous fat, a cellular infiltrate which extended between the individual fat cells and separated them from one another (fig. 1). The vast majority of cells were polymorphonuclear leukocytes. In addition, there were a few histiocytes. The histiocytes tended to lie at the periphery of the fat cells. An occasional histiocyte presented a foamy cytoplasm. In several areas the fat cells were undergoing liquefaction necrosis. The number of leukocytes in the necrotic areas was small, however, and no abscess formation was noted (fig. 2).

The older lesion, fifteen days old, showed an infiltrate which was similar in arrangement to that of the early lesion. The type of cells, however, differed. No polymorphonuclear leukocytes were seen. Nearly all the cells were histiocytes (macrophages). Only a few lymphocytes were present. The majority of the

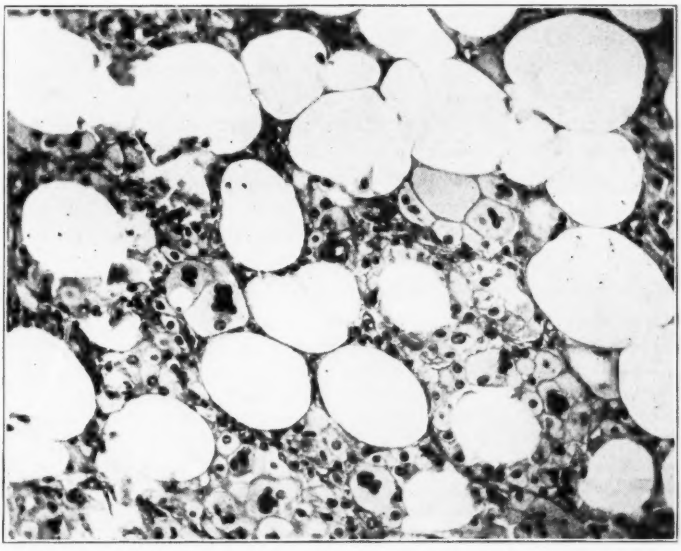

Fig. 3.—Lesion fifteen days old. The infiltrate is composed almost exclusively of histiocytes (macrophages) with foamy cytoplasm. Many of these cells are multinuclear. × 200.

macrophages had a foamy cytoplasm and many were multinuclear (fig. 3). The foamy cells in some areas showed a tendency to pseudoglandular arrangement around the fat cells. The endothelial cells lining the vessels were prominent. In one vessel the endothelial cells had a foamy cytoplasm. Several thick strands of collagen traversed the subcutaneous fat, dividing it into variously sized lobules.

COMMENT

Practically no agreement exists about the initial histologic change in relapsing febrile nodular nonsuppurative panniculitis. Some authors stated that they regarded the invasion and digestion of fat cells by

macrophages as the primary event.[2] Others expressed the belief that the earliest lesion consists of an infiltrate composed not only of macrophages, but also of other inflammatory cells, especially lymphocytes.[3]

Shaffer [4] reported the results of histologic examination of a lesion two days old. He found an infiltrate composed only of round cells; a six day old lesion in the same patient contained, in addition, numerous macrophages.

Ungar [1] found, in a lesion less than twenty-four hours old, an abundant, diffuse infiltrate of polymorphonuclear leukocytes. He interpreted the infiltration as one of suppurative inflammation, despite the fact that there was no abscess formation. In a lesion five days old he observed the typical granulomatous infiltrate with many macrophages. He concluded that the lesions of Weber-Christian disease progress through the following three stages: (1) suppurative inflammation, (2) granuloma-like change with many foam cells and (3) fibrosis.

In the present case biopsies were performed on a lesion less than twenty-four hours old and on one fifteen days old. The early lesion showed an infiltrate composed predominantly of polymorphonuclear leukocytes; only a few foam cells were present. The older lesion showed numerous foam cells and beginning fibrosis; polymorphonuclear leukocytes were absent.

Although the presence of polymorphonuclear leukocytes within the characteristic granulomatous infiltrate has been noted by many observers,[5] the number of these cells has usually been small. Only

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2. (*a*) Cummins, L. J., and Lever, W. F.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Report of Two Cases, Arch. Dermat. & Syph. **38**:415 (Sept.) 1938. (*b*) Binkley, J. S.: Relapsing Febrile Nodular Nonsuppurative Panniculitis: Report of Case, J. A. M. A. **113**:113 (July 8) 1939. (*c*) Tilden, I. L.; Gotshalk, H. C., and Avakian, E. V.: Relapsing Febrile Nonsuppurative Panniculitis: Report of Two Cases, Arch. Dermat. & Syph. **41**:681 (April) 1940. (*d*) Larson, C. P., and Ootkin, B. N.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), Am. J. Clin. Path. **11**:781, 1941. (*e*) Spain, D. M., and Foley, J. M.: Nonsuppurative Nodular Panniculitis (Weber-Christian's Disease), Am. J. Path. **20**:783, 1944.

3. (*a*) Bailey, R. J.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), J. A. M. A. **109**:1419 (Oct. 3) 1937. (*b*) Miller, J. L., and Kritzler, R. A.: Nodular Nonsuppurative Panniculitis, Arch. Dermat. & Syph. **47**:82 (Jan.) 1943. (*c*) Larkin, V. deP.; DeSanctis, A. G., and Margulis, A. E.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Review of Literature with Report of Case, Am. J. Dis. Child. **67**:120 (Feb.) 1944.

4. Shaffer, B.: Liquefying Nodular Panniculitis: Report of Case, Arch. Dermat. & Syph. **38**:535 (Oct.) 1938.

5. Cummins and Lever.[2a] Larson and Ootkin.[2d] Spain and Foley.[2e] Bailey.[3a] Christian, H. A.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Arch.

Weber [6] noted a conspicuous admixture of polymorphonuclear leukocytes within the granulomatous infiltrate. Netherton [7] stated the belief that two types of reaction may occur in relapsing febrile nodular nonsuppurative panniculitis: an acute, leukocytic reaction, as described by Weber, and a chronic type, as reported by Christian and others.

Ungar's case and the present one are thus the only cases in the literature at the time of this report in which the infiltrate was composed almost entirely of polymorphonuclear leukocytes. As, in both cases, this type of infiltrate was present in the lesions less than twenty-four hours old but not in lesions several days old, it may be concluded that the leukocytic infiltrate occurs only in the very early lesions. That a leukocytic infiltrate has not been described oftener is probably due to the fact that these are the only cases in which biopsy was performed on lesions less than twenty-four hours old. It is quite possible that, if in future cases biopsy is performed on very early lesions, a polymorphonuclear infiltrate will be found oftener than hitherto in the initial stage of the disease.

SUMMARY

In a case of relapsing febrile nodular nonsuppurative panniculitis, a biopsy was performed on a lesion less than twenty-four hours old. The histologic picture showed an infiltrate composed almost entirely of polymorphonuclear leukocytes.

This supports Ungar's contention that an infiltrate of polymorphonuclear leukocytes represents the earliest histologic change in Weber-Christian disease.

Int. Med. **42**:338 (Sept.) 1928. Hartwell, A. S., and Thannhauser, S. J.: Case Presentation and Discussion of Relapsing Febrile Nodular Nonsuppurative Panniculitis, Bull. New England M. Center **2**:362, 1940. Ziegert, H. J.: Ein Fall von fieberhafter Wucheratrophie des Fettgewebes (Weber-Christian'sche Krankheit), Zentralbl. f. inn. Med. **61**:610, 1940. Arnold, H. L., Jr.: Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Preliminary Report of Case Controlled by Sulfapyridine, Arch. Dermat. & Syph. **51**:94 (Feb.) 1945.

6. Weber, F. P.: A Case of Relapsing Non-Suppurative Nodular Panniculitis, Showing Phagocytosis of Subcutaneous Fat-Cells by Macrophages, Brit. J. Dermat. **37**:301, 1925.

7. Netherton, E. W., in discussion on Bailey.[3a]

CONTACT DERMATITIS

Practical Management and Identification of Cause Without Patch Testing

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IF THE physician on examining his new patient identifies uncomplicated contact dermatitis, his problem of obtaining a cure has begun to take form. Those familiar with older writings on the treatment of "eczema," containing their detailed expositions of when to use soothing agents, when to use stimulating ones and which species of tar and what concentrations thereof one should employ, can recognize that the philosophy was that a cutaneous disease can be cured, the word "cured" being transitive and the word "disease" implying a concrete thing to be pushed about by means of medicines. This philosophy of the nature of healing is the analogue of the Aristotelian concept of motion as a condition requiring force for its maintenance. Modern dynamics conceives motion as a continuous state which requires a force to alter it, as expressed in Newton's first law. Return to health is, I think, to be considered the normal tendency which requires an interfering agency to prevent it. Thus cure is obtained, not by treating a disease, but by counteracting such forces as prevent healing. My mode of attack is based on the assumption that an injured tissue heals if and when it is not again injured. Cure in contact dermatitis may be said to have been accomplished if (*a*) the patient is free from disease, (*b*) the provocators of disease have been identified and (*c*) the patient has been taught to achieve a normal way of life by avoiding provocators and by using such safe substitutes as are needed.

ELIMINATION OF CAUSE

The necessity is plain, and it is trite to reiterate it, that the cause must be eliminated if relief is to be got. Journals and books are full of descriptions of procedure, enjoining on the physician his need to be a Sherlock Holmes, insisting that the only effective treatment of contact dermatitis involves the detection of the irritant. But it is not true that the cause must be known before recovery may be obtained. It is easier, I have found, first to eliminate the cause without knowing what it is and

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Canada, June 6, 1947.

then to identify it specifically after the skin has healed. The method I present is simple and renders superfluous, in most cases, preliminary detective work, crystal gazing and multitudinous cutaneous tests, "reproductive," if one has guessed well, "of the disease in miniature under controlled conditions."

When the patient is first seen, suffering, let us say, from itchy eyelids and face, the fact is that no one, patient or doctor, knows what chemical causes the disease. One does know, however, that the causative chemical must touch the skin, be it constantly or infrequently. One therefore orders the patient to let nothing touch the skin excepting those chemicals which are entirely trustworthy and not open to suspicion. These are the safest and most trustworthy chemicals:

(1) air, if it is not contaminated with soap particles, perfume or such

(2) water

(3) petrolatum (not invariably "safe")

(4) cellulose, such as in cleansing tissues, cotton or linen uncontaminated with such things as soap, dye, starch or fabric finish

(5) hands (which are going to touch an itchy skin, one may be sure), if they are not contaminated with nail lacquer, cold cream, soap or the like

(6) selected textiles: a textile, including garments for day and night wear, may be judged "safe" if it was touched repeatedly without harmful effect during a six month period prior to the onset of dermatitis. I request the patient to sort his textile contacts, item by item, into two groups by this criterion. He wears and touches the "safe" ones only and sets aside the doubtful ones until the time comes for testing items later.

No medication is so trustworthy as petrolatum and cotton towels moistened with cool water. These agents do yield relief and may be used so as to give comfort. Some dermatologic authorities would make patch tests with ingredients of proposed medicines. This is not worth doing when one limits medication to substances nearly always innocuous.

Instructions vary in cases affecting various parts of the body. If contact dermatitis is limited to the scalp, for example, it would be silly to advise the patient to wear predermatitis shoes. One has also to take into account the ecologic aspects. The patient must eat, sleep, be clothed and do certain unavoidable tasks. A wealthy unemployed single woman presents an entirely different problem from the housewife who is economically incapable of hiring help and who is responsible for three small children and an ailing mother. One must give instructions which can be carried out. The patient is asked for a maximum of two weeks of intensive effort at eliminating contactants, for this is long enough to do the work and short enough to get cooperation. The patient is caused to understand that elimination means 100 per cent and that 99 per cent is not good enough. Even obtuse patients, if not hopelessly stupid, can be induced to comprehend.

OUTLINE OF ELIMINATION TECHNIC BY LOCATION OF DISEASE

Dermatitis Limited to the Scalp.—Omit medication, shampoo, lacquer, hair tonic, brush, hat, hair pins, perfume, barber shop or beauty parlor. See that hands do not convey an irritant, such as nail lacquer. Cleanse scalp and hair by prolonged spraying or showering with tap water.

Dermatitis Limited to the Face.—Omit medication, every toilet article and cosmetic, soap, dentifrice, mouthwash and eyewash. See that hands do not convey an irritant to the face. Cleanse with water and petrolatum. Brush teeth with baking soda. Shave with an electric shaver. Wash dishes with a nonsudsing cleanser, such as "sutho," so that bursting bubbles do not contaminate the air. Eliminate textile, scalp and neck contactants.

Dermatitis Limited to the Neck.—Omit medication, every toilet article and cosmetic, soap, perfume, and jewelry which may touch the neck. Eliminate textile and face contactants. See that hands do not convey an irritant to the neck. Cleanse with water and petrolatum.

Dermatitis Limited to the Region of the Trunk.—Omit medication, every toilet article, soap and cosmetic which touches the trunk. Control textile and neck contactants and those conveyed by hands. Check metal fasteners, menstrual accouterments, contraceptives, matches, dress shields, bust pads, cleansing or antiseptic agents applied to the bath tub, rubber pads and hot water bottles, insecticides and cleaning fluid or starch (which contains borax) in textiles which would escape if their safety were judged solely by their age. Soap used for enemas may maintain perianal dermatitis when the patient bathes only with water. Cleanse with water. Use cornstarch for powder and baking soda for underarm deodorant. Use petrolatum on babies, not olive oil or antiseptic oils.

Dermatitis Limited to Feet and Legs.—Omit medication, soap, depilatory and leg makeup. Control textile contactants and those conveyed by hands. Judge shoes and slippers by the same criteria as textiles. Check for weeds, irritant dusts, floor waxes, paints and cleansers. Women rarely possess "safe" old stockings; they may risk the purchase of cheap cotton hose. Soap splashed from the washing machine may irritate legs. Nail lacquer is sometimes applied to runs in stockings. Presumably "safe," old shoes may be contaminated with medication. One may buy a pair of new shoes and wear them exclusively; either they are harmless and the foot disease fades, or they are not and the feet get steadily worse, so that security of the foot gear may be judged positively.

Dermatitis Limited to Distal Upper Extremity.—Omit medication and all cosmetic and toilet articles which may touch the hands. Control face and scalp contactants, for these are applied with the hands, and hair tonic and cold cream may irritate hands without irritating the head. Cleanse hands and body (hands must hold the soap to wash other parts) only with water and petrolatum. Wash dishes with hot water only, or delegate the job without drying dishes which have been washed with soap by others. The patient should wash her babies only with water for the two week period. Stop baking, for flour often irritates. Omit every household cleansing and polishing agent. Omit gloves, including rubber gloves. Judge purses by criteria of "safe" textiles. The usual irritants of hands are cleansing agents and toilet and cosmetic articles. However, paints, paint remover, plants, sprays, materials for all sorts of needlework, chrome, nickel and lacquered fasteners, gewgaws and gadgets, chemicals met in hobby, business or recreation—all are open to suspicion. Employees may have to be taken off the job in order to eliminate the unknown contactant.

Cases of dermatitis of the hands are harder to solve than others, but the reason for this proves usually to be that the dermatitis is not purely contactant. Dermatitis of the hands often involves also focal and secondary infection and sometimes food allergy.[1] I believe that few cases of dermatitis of the hands of two or more months' duration are of uncomplicated contact dermatitis. Occlusive dressings may be used, of course, and, if improvement is not obtained in a week, complicating factors may be assumed to exist.

Dermatitis Affecting the Skin in More Than One of the Listed Limited Regions.—Since any distribution is a sum of some combination of the limited distributions already considered separately, simply add together the elimination efforts for each region involved.

So one seeks, and may readily obtain, 100 per cent elimination of all possible causes. As a result the disease fades and does not flare. If a flare occurs, elimination (or diagnosis) has not been successful, and restrictions must be reviewed. Useful information is obtainable from flares, for contact with the injurious chemical must have occurred within a few hours prior to the inception of the flare.

PROOF OF ELIMINATION OF CAUSE

It rarely requires more than a week to obtain demonstrable elimination of an unknown contactant cause. Proof of successful elimination rests on observation of uninterrupted improvement. If the skin is healing, one knows that the poison has been kept off. Therefore, among the things which have been kept off, at least one is a poison.

IDENTIFICATION OF CAUSE

The patient is then requested to write a list of things which he desires to touch and which have been denied. He is instructed to make his usual contact with these agents, not in a hit or miss way, but by contacting one agent of the list, and one only, each day. Not many patients desire to touch more than six to a dozen agents which were denied during the period of complete isolation. By reapplying to the skin systematically all of those items denial of which was followed by healing, one inevitably reapplies the poisonous one, which is identified by the promptly resultant flare of itching and disease. The patient knowns how to achieve recovery from this flare, how to live without the injurious item and how to find a safe substitute for it.[2]

COMMENT

The simplicity of this scheme is such that one wonders why it has not previously been adopted. Elimination of contactants according to "the

1. Winston, B. H.: Dermatitis of the Hands, Arch. Dermat. & Syph. **57**:357-367 (March) 1948.

2. Sutton, R. L., Jr.: Contact Dermatitis: Simplification of Therapy and of Search for Causes, J. Missouri M. A. **44**:481-484 (July) 1947.

literature" and to the practices of physicians whose failures I have observed—including my own—generally takes the form of guessing that the noxa may be nail lacquer, face powder or something else, whereupon patch tests are made with the suspicious item, or it is omitted, or a substitute is prescribed. In doing this the error lies in trying to determine the cause first when one is not ready; one should learn to walk before attempting to run. Mine is a simple and direct procedure to eliminate all possible causes, clear the skin and then add one contactant at a time, in its usual form of contact, with its usual site of application and with the usual unfractionated contactant, until flare identifies an irritant. This avoids the many pitfalls recognized in patch testing.

Patients are delighted with the logic and simplicity of their treatment. The physician commands the situation from the start; he possesses a "forced win." Symptomatic relief is as good with petrolatum, cool aqueous compresses and perhaps acetylsalicylic acid and amobarbital sodium (sodium "amytal") as it is with formulas that cannot be written on one side of a prescription blank. The procedure is based on fact, the elementary truth being that at first one does not know the cause, knowing only that the cause lies within the class of objects which come in contact with the skin.

Difficulties occur when contacts believed to have been eliminated nevertheless are made. A woman with itchy eyelids, who cooperated intelligently, experienced a flare-up after playing cards. I learned that the sizing of the washable cards was carried to the face by the fingers, previously imagined to be not contaminated. Another woman with dermatitis of the face from menthol experienced a flare-up when she sucked certain cough drops. A man with dermatitis of the dorsum of the left hand was observed, after no little investigation, to be intolerant of the dentrifice with which he cleansed his dentures, which he held in the left hand and rinsed with the right before returning them to his mouth. One must be alert to chemicals put into ears, eyes, nose, mouth, rectum or vagina. The expert learns to be aware of all the things that persons of various ages and both sexes do and touch.

Difficulties occur when the contactant is an occupational one, when the patient, if he is to be on the job at all, must make contact with many possibly harmful chemicals and by the nature of the situation cannot limit his renewed contacts with them to one item a day. The disease in such patients can be proved occupational by (1) excluding all contactants except occupational, (2) observing that the disease continues and then (3) removing the patient from the job and finding that the disease disappears. Prior to returning the patient to his job, patch tests with chemicals met occupationally are an obvious help. Other cases do come up wherein the peculiarities of the puzzle render my method of detecting

causes not the easiest way, but in my practice these are exceptional. I am not prepared to say categorically that patch testing in contact dermatitis may be wholly dispensed with. I say, however, that at least a great deal of patch testing may be neglected and that the practice of dermatology may thereby be improved in efficiency to a notable degree.

Failures occur when the disease is not pure contact dermatitis. Secondary infection must be recognized and dealt with by means of nonirritating antiseptics. Primary infections may simulate contact dermatitis. Foci of infection may profoundly influence what starts as contact disease. In chronic dermatitis of hands or feet especially, the elimination of contactants combined with the elimination of focal infection comprises an attack which is often curative.[2] Atopic dermatitis does not yield to elimination of contactants, although such elimination contributes to the patient's welfare.

SUMMARY

Contact dermatitis is an injury of the skin which heals spontaneously if, and only if, the skin is not again injured. Medicines do not make it heal. It is not necessary to know the cause before eliminating it. The technic is discussed of enabling the patient to eliminate all possible causes until the skin heals. Then suspicious contacts are replaced, not by patch testing, but by actual use, item by item, until flare identifies the irritant. Selection of agents for patch testing requires guesswork, howsoever canny. This method does not.

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ABSTRACT OF DISCUSSION

DR. JOHN G. DOWNING, Boston: I agree with Dr. Sutton that the first essential is the identification of the disease. Contact dermatitis is not always easy to diagnose; it may simulate almost any dermatologic entity. With the diagnosis established, complete elimination of all possible factors is the aim of all dermatologists at the first visit. There are no safe or trustworthy chemicals, and initial careful history should reveal the possible allergens. Sensitization may appear after months or years of contact.

In my experience many chemicals produce fairly characteristic eruptions. With the history and observation one can reassure a patient by planning a fairly normal existence with only a few deprivations. If it takes a week for elimination, then the patient is usually safe for testing, so that no time is gained or lost. By that time, proper deduction and thorough study of the patient and his surroundings may have eliminated the necessity of patch tests or at least should have reduced them to a minimum. Replacing one contact at a time is valuable in persons with limited contacts but impossible in occupational exposures. Patch testing in industry not only helps the injured employee but may prevent others from being affected. Patch tests when indicated are still of value in detecting the allergen of contact dermatitis. Taking a complete history and proper patch testing should prevent flare-ups, which frequently are worse than the original attack.

Dr. Sutton's outline of instructions by location of disease is excellent. I would be interested to know how it was determined that the menthol, rather than the usual essential oils used in cough drops, was the causative factor in the case noted.

I agree with Dr. Sutton that true contact dermatitis will heal without medication. Most patients are overtreated, for nature will regulate the course of the disease, provided that nothing interferes. However, scratching because of pruritus must be controlled, and all who have suffered from a pruritic eruption realize that it needs more than plain water to relieve it. Soothing medication is still popular with my patients.

Dr. Marion B. Sulzbegrer, New York: When one sees a case of contact dermatitis, localized or not, one tries, by history taking and common sense, to find the substances which are most suspect and then to eliminate those substances. That is the first step in every approach. I submit that the procedure which Dr. Sutton follows is not so very different from that. It enumerates the suspected substances and tells the patient to eliminate them. If one is successful in that attempt, the contact dermatitis, under whatever mild treatment is chosen, usually clears up.

By study and interrogation of the patient one ascertains a certain number of items which are suspect. After compiling such a list I think that it is often simpler to make patch tests with the suspected agents, note results and thus find which are most suspect than to try to reexpose the patient repeatedly to each of the sometimes very numerous items. The patch test is a shortcut, a method used to narrow down the field and focus attention on those items which are most likely causes among those open to suspicion.

Of course, when the results have been obtained, one must check them by what happens when the patient avoids the substances which produce the positive reactions and perhaps eventually, if necessary, by seeing what happens on reexposure.

I think that Dr. Sutton has proposed a formidable and utopian program when he advocates the elimination of all suspected substances. As Dr. Downing said, there are no safe agents. I know of patients who have reacted to the agents that Dr. Sutton has described as safe, for instance to petrolatum or to paper towels. There are simply no absolutely safe manufactured products in our complicated existence. All clothing contains not only the material of which it is woven but dyes, mordants, sizing, weighting and perhaps a large variety of other substances of which dermatologists do not even know today; bottle caps, paper towels and necklaces can contain formaldehyde, and "safe" certified food colors may contain iodine and bromine.

Therefore, to say that one can put a person into a safe atmosphere appears to me a fantasy. I conceive it to be much more simple and logical to reduce the exposures to suspects by common sense methods and to endeavor to find out those exposures which on removal lead to improvement or cure and, in the event of many suspects, to find the most suspect by employing every procedure and shortcut, including patch testing and, if necessary, the reexposure test.

Dr. H. J. Templeton, Oakland, Calif.: The only fault in Dr. Sutton's technic is one peculiar not to dermatologic problems but to medical problems in general; that is to say, such an approach requires intelligence on the part of the patient. One of the most discouraging things that can happen to a dermatologist is to spend a half-hour or more with a patient, telling him what contact dermatitis is and explaining to him the Sutton method and then have him say, "But, Doctor, what is the cause of my trouble? Is it acid in my blood?" A limitless amount of time and patience is needed when dealing with such a patient.

DR. EARL D. OSBORNE, Buffalo: When Dr. Sutton started his presentation, he somewhat belittled the attempt at the detective approach to this problem, but I submit that Dr. Sutton exemplifies a superdetective. I agree regarding petrolatum. I think that if one investigates that problem one may find a number of persons who react to one or the other of the petroleum derivatives.

If the responsible agent is found, I think that it is still fallacious to think that the contact dermatitis will clear up in a period of a month or six weeks. I have seen a number of cases of contact dermatitis that persisted for months following that period. There are many cases of contact dermatitis that do not clear up in a short period.

I think that one of the problems in contact dermatitis and one of the most worth while studies at the present time is to determine by microchemistry or some other method how long certain substances remain fixed in the epidermal layers. There is evidence, particularly with chromium and nickel metal, that the albuminous metal substance remains for long periods. If one could eliminate that substance from the skin, it would greatly facilitate treatment and would help in some of the most resistant cases of contact dermatitis.

DR. GEORGE M. LEWIS, New York: I should like to call attention to the irreversibility of the eczematous process when the dermatitis has remained over a period of time, because of repeated insults to the skin. In other words, simple withdrawal from contact with the sensitizing agent will not necessarily bring about spontaneous cure; often, local therapy, including roentgen therapy, and occasionally weeks and months of freedom from contact with any and all irritants and sensitizers are required.

DR. CHARLES C. DENNIE, Kansas City, Mo.: I have just three points: Be good detectives; break down the wall of resistance pathologically and do not tell the patients anything.

DR. RICHARD L. SUTTON: Dr. Downing, of course there is difficulty in identification of the disease as pure contact dermatitis. I think that we can agree that there are instances in which patch tests are valuable. There is no denying that there are situations when they are utterly necessary, particularly in identifying the particular ingredient of some substance which has proved injurious. However, identifying the particular ingredient is not necessarily of interest to me in the simple practice of medicine. When a certain cosmetic cream is responsible I do not have to know the particular ingredient. I have only to know that a certain substitute will handle the situation, and the patient is satisfied. As for symptomatic relief with water and petrolatum, I am satisfied that those two agents will give relief. When one uses water compresses, one must use a "safe" towel. I insist that cellulose is safe and agree that paper towels are not necessarily safe. One applies cold water for as long as it feels good, any time one wishes, and it does relieve the itching and kills time long enough for the patient to recover.

I agree with Dr. Sulzberger that all of us do treat patients fundamentally in the same manner. His remarks would be more usefully directed to those physicians who fumble the problems before the patients come to dermatologists in desperation.

The pitfalls of patch testing would require a separate thesis of considerable extension. Among them is the fact that contact dermatitis includes primary irritants and physical agents as exciting causes of dermatitis, and one does not find them by patch testing. A man may be able to tolerate soap five times a day but not twenty times a day. I think that one can find that out by my method.

In regard to clothing and the definition of "safe" clothing, I say again that this definition is a practically secure one and enables the patient to sort his clothing. One sets a date for the onset of the dermatitis and assumes that the clothing which was old at that time is "safe" clothing. All other clothing is not safe. Old clothing can be contaminated, of course, with cleaning fluid, soap and other things, but I do not believe that it often happens that a person wears something for a year and then becomes sensitive to it.

Intelligence on the part of the patient is desirable, of course. However, if one takes all the suspect contacts away, even unintelligent patients sometimes understand.

Persistence of contact dermatitis for a month after removal of contact is not remarkable in dermatitis due to metal, but if the disease develops a month after the last contact, that time interval is too long. If many months elapse between the last contact with the initially causative chemical and the disappearance of disease, then some complicating factor surely exists. This factor is usually inept treatment or focal infection. In treating any chronic dermatitis the actual elimination of contactants together with all focal infection surprisingly often proves curative.

INTRAEPIDERMAL BASAL CELL EPITHELIOMA

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IN THE PAST, the basal cell epithelioma has been discussed in great detail by a multitude of writers, who have centered their attention chiefly on the usual varieties, in all their clinical manifestations. For the most part, differences in the clinical picture have accompanied, with minor variations, approximately the same differences in the microscopic picture. In the following paper we present a rather rare type of basal cell epithelioma, namely, intraepidermal basal cell epithelioma.

The first known case of intraepidermal basal cell epithelioma was described by Borst.[1] While studying routine serial sections taken for biopsy from the border of an ulcer of the lower lip, he noted a peculiar formation within the epidermis. The usual microscopic picture of basal cell epithelioma was seen at the ulcerated portion, and at points quite distant from this area, but within the boundaries of the epidermis, were islands of abnormal cells. The cells were larger than normal and deeply basophilic in their staining characteristics. The nuclei presented many mitotic figures. In some areas the cells showed a remarkable behavior. The basal cells appeared as normal cylindric cells, whereas immediately above at the basal margin the entire epidermis was replaced by pathologic cells. Most important was the fact that the zones farthest from the basal margin were the least involved. In other words, the growth was upward rather than downward, in the usual manner. Borst stated that he had never seen anything like this, except in the changes of Paget's disease (carcinoma simplex of the nipple). The question arose whether the changes in his case were primary (i. e., multilocular original growths) or secondary (i. e., growths all arising from one site by extension of the primary tumor). Borst contemplated the theory that they were primary, because of the great distance from the original growth, without disturbance in the corium, and the fact

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1. Borst, M.: Ueber die Möglichkeit einer ausgedehnten intraepidermalen Verbreitung des Hautkrebses, Verhandl. d. deutsch. path. Gesellsch. **7**:118, 1904.

that the entire process did not invade the cutis but remained within the normal margins of the epidermis. On the other hand, he supported the theory of secondary extension from the original growth because of his past experience in noting extension within the epidermis, with final extension down into the cutis. Nevertheless, he did express surprise and remark on the extreme rarity of such a growth remaining entirely confined within the limits of the epidermis, with its only extension toward the surface, rather than into the cutis, in the usual manner.

Jadassohn [2] first brought this rare condition into prominence when he cited Borst's case and reported his own. Clinically, his case was atypical in every respect: Lesions of various sizes were scattered over the trunk, simulating those of lupus erythematosus or of psoriasis. Histologically, his observations were noteworthy. In the middle of the rete pegs, in a multicentric pattern, were nests of epitheliomatous basal cells, all sharply outlined and made up of swollen, darkly stained cells. Jadassohn stated that this pattern is proof of the intraepidermal origin of the basal cell epithelioma. He also described a similar picture in the wall of a follicle. Whereas Borst's conception was that of a unicentric origin of the intraepidermal basal cell epithelioma, Jadassohn expressed the belief that the tumor was of multicentric origin.

In 1920 the lesion was described again by Rose.[3] Clinically, Rose's patient presented many small, pink lesions over the midline of the abdomen, the buttocks and the scapular areas. Microscopically, the epidermis revealed little outside the pathologic area. In one place a peglike or bottle-shaped formation was noted. Within the necklike portion of this mass was a group of deeply stained cells, which branched somewhat and projected upward toward the surface. There was no hair or keratin within the cavity of the mass. The corium revealed no unusual characteristics. Rose concluded his paper by stating:

> Whether this formation is a preformed follicle or part of a tumor which has remained within the epidermis is difficult to determine definitely.

The appearance was that of a tumor within the wall of the follicle, or of a growth shaped like a follicle, but not spreading into or through the cutis.

Bowen,[4] Cheatle,[5] Whitfield,[6] Davies,[7] Fraser [8] and Wise [9] all discussed one form or another of superficial epitheliomatosis. None of them, however, gave a complete discussion of intraepidermal basal

2. Jadassohn, J.: Demonstration von selteneren Hautepitheliomen, Beitr. z. klin. Chir. **136**:345, 1926.

3. Rose, K.: Ueber Rumpfhaut-karzinome, Inaug. Dissert., Breslau, 1920.

4. Bowen, J. T.: Precancerous Dermatoses, J. Cutan. Dis. **30**:241, 1912.

5. Cheatle, G. L.: Desquamative and Dysgenetic Epithelial Hyperplasias in the Breast, Brit. J. Surg. **13**:509, 1925-1926.

cell epithelioma. Montgomery,[10] in an excellent review of the entire subject of epitheliomatosis, discussed 5 cases which he collected, and which may be classified with the intraepidermal epitheliomas. In these cases a mixture of basal cell epithelioma and prickle cell epithelioma, confined within the normal margins of the epidermis, was noted. The author, rather than confuse the issue by establishing another category, classified the cases in the group of superficial epitheliomatoses. Fraser [8] once included Bowen's disease with intraepidermal epithelioma, but later, in a communication to Montgomery, admitted that it is a separate entity. Ormsby [11] described intraepidermal basal cell epithelioma as a rare type of basal cell epithelioma with a "reversed" growth, growing upward into the epidermis rather than downward, in the usual manner.

REPORT OF CASES

In the present paper, we report 3 cases in which the picture meets the requirements of an intraepidermal basal cell epithelioma.

CASE 1.—Macroscopically (clinically), M. M., a white woman aged 52, presented a slightly lichenified and clearly demarcated plaque situated dorsally at the junction of the third and fourth fingers. Microscopically, the epidermis was irregular, and composed of elongated and rather broadened rete pegs. The surface was covered for the most part with a horny layer of moderate thickness, and the remainder, with parakeratotic lamellas. At many points within the epidermis were rather large cells, which were round, oval or oblong and between which the "prickles" could not be observed. These cells stained more intensely with the basic stain than do normal prickle cells. Scattered mitotic figures were observed. The upper portion of the corium presented dilated vessels. A diffuse, nonspecific cellular infiltration, consisting of small round cells, could be seen in the upper part of the corium, whereas the collagen in this zone presented moderate interstitial and parenchymatous edema.

CASE 2.—Clinically, A. M., a white woman aged 48, presented groups of crusted, erythematous papules over the center of the abdomen. When the crusts were removed, slight bleeding occurred. Microscopically, the epidermis was thickened and somewhat irregular. The rete pegs for the most part were elongated and broadened. Within the epidermis were numerous masses of round,

6. Whitfield, A., in discussion on Savatard, L.: Ichthyosis and Cancer of the Skin, with Special Reference to Mulespinners' Cancer, Proc. Roy. Soc. Med. (Sect. Dermat.) **20**:93, 1927.

7. Davies, J. H. T.: Bowen's Disease, Proc. Roy. Soc. Med. (Sect. Dermat.) **20**:111, 1927.

8. Fraser, J. F.: Bowen's Disease and Paget's Disease of the Nipple: Their Relation to Dyskeratosis, Arch. Dermat. & Syph. **18**:809 (Dec.) 1928.

9. Wise, F.: Multiple Superficial Benign Epithelioma of the Skin, Arch. Dermat. & Syph. **19**:1 (Jan.) 1929.

10. Montgomery, H.: Superficial Epitheliomatosis, Arch. Dermat. & Syph. **20**:339 (Sept.) 1929.

11. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 698.

oval and, in some instances, polygonal cells. The last type took the basic stain. Scattered islands of relatively normal prickle cells were present. The basal cell layer was apparently intact throughout the section. The corium presented dilated, congested vessels in the papillary zone. A diffuse, nonspecific cellular infiltration of small round cells, wandering connective tissue cells and plasma cells was observed in the upper portion of the corium. The collagen of this zone presented moderate interstitial and parenchymatous edema.

CASE 3.—J. A., a white man aged 57, gave a history of having had a "mole" at the site of the present lesion burned off several years ago. The present

Fig. 1 (case 3).—Section showing dark-staining intraepidermal masses of basal cells.

lesion was approximately the size of a 25 cent piece and was situated over the right temple. It had the following clinical characteristics:

It was raised, with a central depressed, crusted, ulcerated area, approximately the size of a 5 cent piece (75 mm. in diameter). The borders were nodular, with many fine telangiectases. The entire lesion was sharply demarcated, with a faint, erythematous surrounding area.

Microscopically, the epidermis was somewhat irregular and covered in part with an ulcerated, laminated horny layer. At various points within the epidermis were dark-staining, fairly well defined cellular masses of varying sizes,

composed of cells some of which were oblong, others round and still others oval. The nuclei were round or oval and usually contained one or two nucleoli and a pale-staining chromatin network. Most of these masses were surrounded by rete cells and were, therefore, intraepidermal. Occasional mitotic figures could be noted. The corium revealed a mild, diffuse cellular reaction, composed of small round cells, wandering connective tissue cells and plasma cells. The vessels were somewhat dilated, with a moderate amount of edema of their walls. Some basophilic degeneration of the collagen fibers of the upper portion of the corium was noted.

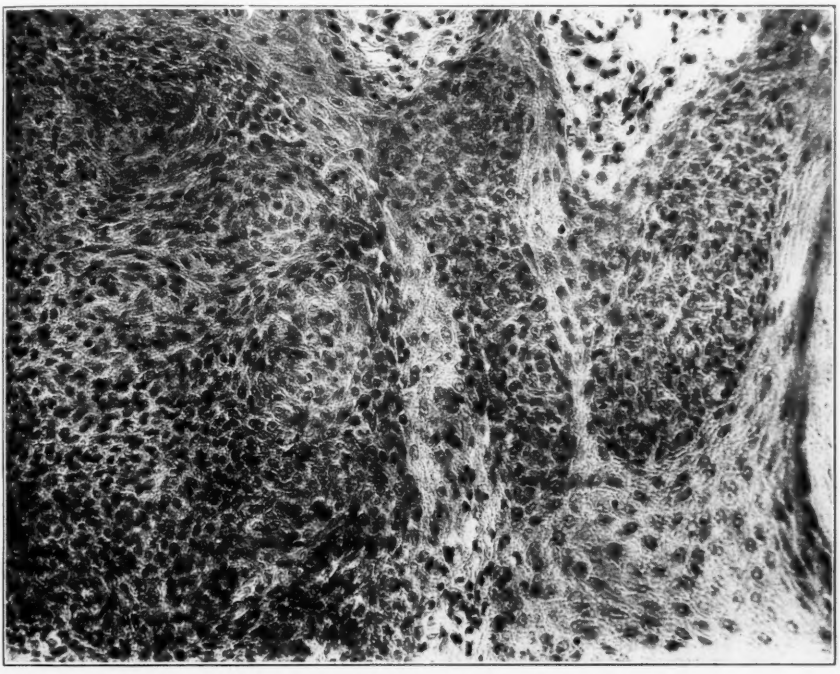

Fig. 2 (case 3).—High power of field shown in figure 1.

SUMMARY

The literature regarding intraepidermal basal cell epithelioma is reviewed.

Three cases of this comparatievly rare entity are described.

Intraepidermal basal cell epithelioma presents a characteristic histologic picture.

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METASTATIC TRANSITIONAL CELL CARCINOMA OF THE PENIS SIMULATING A CHANCRE

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CANCER of the nasal pharynx comprises a small percentage of all malignant growths of the head and neck. It has a high incidence of occurrence in male subjects (about 80 per cent)[1] and has a tendency to occur at a younger age than does cancer in other regions of the upper part of the respiratory and alimentary tracts. Statistical studies indicate that about 7 per cent of all fatal cancers in men originate in the oral region.[2] Tumors of the nasal pharynx, roughly speaking, fall into three groups, namely, carcinomas, sarcomas and endotheliomas. Under the head of carcinomas, many types occur: squamous carcinoma, scirrhous carcinoma, nonepidermoid or basocellularis carcinoma, epidermoid or spinocellularis carcinoma, intermediary epidermoid carcinoma, anaplastic carcinoma, adenocarcinoma, undifferentiated carcinoma, transitional cell carcinoma and lymphoepithelioma.[3] The difference between transitional cell carcinoma and lymphoepithelioma is little, the main difference being the amount of lymphocytic infiltration. They both seem to originate from the transitional epithelium and the lymphoid tissue of the nasopharynx and throat. Thirty-seven per cent of nasopharyngeal malignant growths are of the transitional cell type. This type of cancer is extremely metastatic, and early metastasis to the lymph nodes of the neck occurs. Cervical node enlargement may, in fact, be one of the earliest signs referable to these tumors. That metastatic lesions can occur in other areas is shown by the following case which was seen by us.

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1. Ballenger, W. L., and Ballenger, H. C.: Diseases of the Nose, Throat and Ear, ed. 8, Philadelphia, Lea & Febiger, 1943, pp. 537-540.

2. Beiswanger, R. H., and Stenstrom, K. W.: Carcinoma of the Cheek, Alveolar Processes, Floor of the Mouth, and Palate, Radiology **44**:213-224 (March) 1945.

3. Salinger, S., and Pearlman, S. J.: Malignant Tumors of the Eipipharynx, Arch. Otolaryng. **23**:149-172 (Feb.) 1936.

REPORT OF A CASE

J. B., a 19 year old white youth, entered Wood Veterans Administration Hospital on Jan. 19, 1947, with symptoms of partial intestinal obstruction. This was treated conservatively, and he responded satisfactorily without surgical intervention. A short time after admission, a dime-sized superficial ulcer developed on the dorsum of the coronal sulcus of the penis, which was considerably indurated and slightly elevated above the surface of the skin. Nontender bilateral inguinal lymph nodes from the size of a pea to that of a walnut were present. The shaft of the penis showed a diffuse fusiform enlargement. Clinically, this ulcerated lesion resembled a chancre (fig. 1). The patient was first seen by the department of dermatology on February 4, and in addition to the described lesion of the penis, it was noted that the patient was emaciated and that he showed chronic radiodermatitis of the lower part of the abdomen and of the cheeks. The patient gave a history of having had his last sexual exposure about seven months previously; he had received an unknown amount of penicillin for treatment of a secondary infection of his nose.

On further questioning, it was learned that a growth in his nasal pharynx had developed with enlargement of the cervical lymph nodes about eighteen months

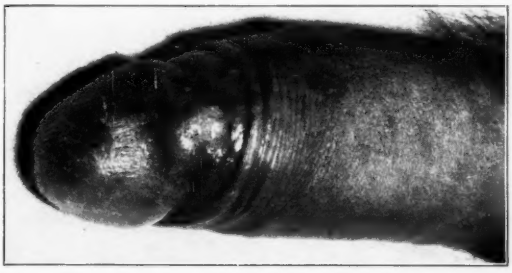

Fig. 1.—Lesion of the penis simulating a chancre and showing fusiform swelling of the penis.

previously. This had been diagnosed as a transitional cell carcinoma by biopsy. At the time the original diagnosis had been made, the patient was at Hines General Hospital, where he received an undetermined amount of radiation therapy. Six months after the treatment of this initial lesion in the nasal pharynx, a similar lesion developed, involving the right maxillary sinus, for which he received a second course of irradiation. After the second course of treatment, the patient received a slight trauma over his upper lip, and within one month there was a swelling of this area. A biopsy again revealed the same type of transitional cell carcinoma, for which he received further roentgen therapy. Examination of the ears, nose and throat showed an absence of the upper incisor teeth and the alveolar ridge. There was a considerable amount of pain and tenderness on manipulation of the upper lip, which was rather swollen; otherwise the oral cavity appeared to be normal. There was some thick purulent discharge on the postpharyngeal wall, and scattered hypertrophied lymphoid tissue was present. Examination of the nose revealed an essentially normal left nasal fossa. There was a purulent exudate from the right middle meatus, which was also present on the floor of the right nasal fossa.

The nasal pharynx was visualized, and no abnormalities were noted. There was slight tenderness over the right maxillary sinus. By anterior laryngoscopic

examination the turbinates appeared normal. There were nontender palpable pea-sized submental glands, and the cervical glands were palpable bilaterally.

The patient gave a history of having had several episodes of intestinal obstruction, which had previously been believed to have been due to metastatic lesions involving the intestines, for which he had received roentgen therapy of high dosages

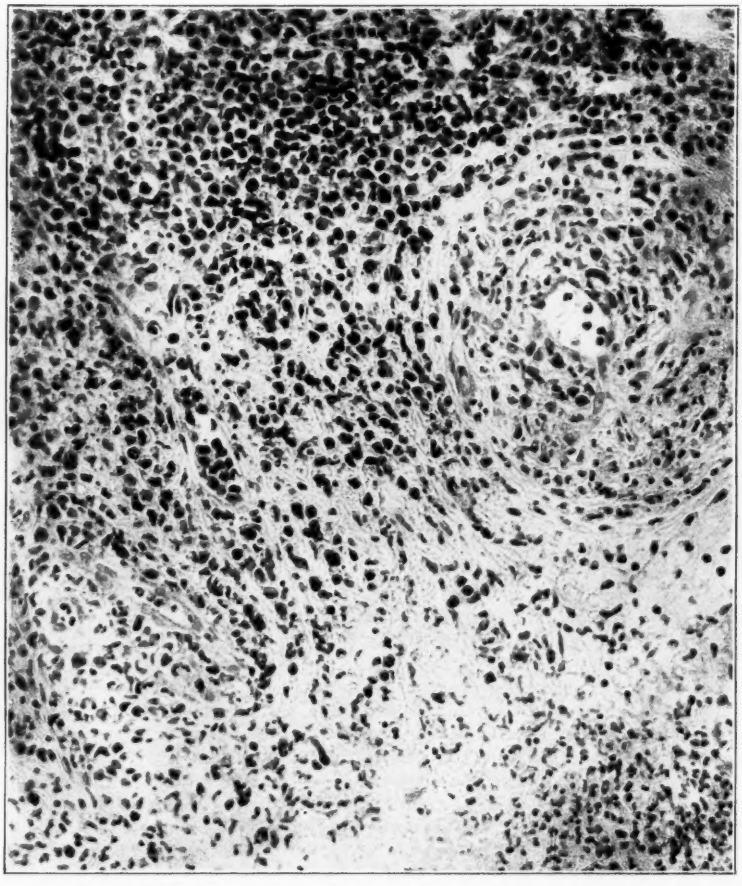

Fig. 2.—Penile lesion. Infiltration of subcutaneous tissue by cords and pavements of undifferentiated epidermoid cells of transitional cell type.

to the lower part of the abdomen. His partial intestinal obstruction had always been satisfactorily controlled by conservative therapy, and at no time had he required surgical intervention.

As the lesion on the penis resembled a chancre, repeated dark field examinations were done. These had negative results on three consecutive days (February 11,

12 and 13). Reactions to serologic tests of the blood (Wassermann and Kahn) were negative on July 26, 1946, Jan. 19, 1947 and February 10, 20 and 28. A biopsy of the penis was done; microscopically the lesion was shown to be a metastatic carcinoma, highly malignant, consistent with transitional cell type (fig. 2). Within a period of three weeks, reddish elevated infiltrated lesions, the size of a quarter, developed, involving the right shoulder, right clavicular area and right thigh. Biopsies of these lesions were done; microscopically they showed metastatic

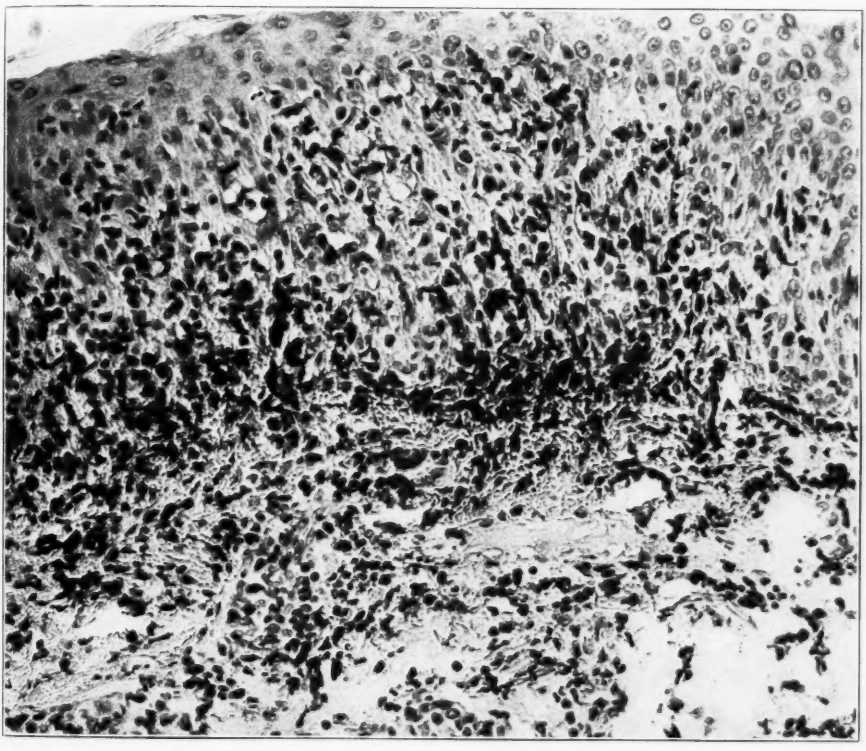

Fig. 3.—Skin. Transitional cell carcinoma infiltrating subcutaneous tissue with extension to the epithelium (hematoxylin and eosin × 400).

carcinoma consistent with transitional cell type (fig. 3). The penile ulceration from which the biopsy specimen was taken failed to heal. Enlarged necrotic areas appeared, involving the glans of the penis. Many more small metastatic cutaneous nodules developed of the back, abdomen and chest. On March 11, the patient again showed signs of a partial intestinal obstruction, which was again treated successfully by conservative methods. In spite of supportive therapy, his hospital course was rapidly downhill and he died on April 12. A postmortem examination was not done.

SUMMARY

A case of transitional cell carcinoma is presented, the primary site of which was in the nasal pharynx, with early metastatic lesions involving the cervical lymph nodes, maxillary sinus and upper lip. These lesions were treated extensively with large doses of roentgen rays. In spite of the roentgen therapy, symptoms developed referable to a partial intestinal obstruction which was thought to be due to metastasis involving the alimentary tract; it was treated again with roentgen rays to the abdomen. Eighteen months after the initial diagnosis of transitional cell carcinoma involving the nasal pharynx, a penile lesion developed clinically resembling a chancre.

As the patient gave a history of having received penicillin after his last sexual exposure, it was thought that this lesion might be a chancre, the appearance of which was delayed by treatment with penicillin. The diagnosis of carcinoma was made by microscopic examination.

CHRONIC SYMMETRIC IMPETIGO

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DURING the past several years I have observed a chronic, benign and mildly inflammatory dermatosis which, because of its occurrence on bilaterally symmetric regions and its resistance to therapeutic measures, seems to merit description. The condition is an exogenic infection with hemolytic Staphylococcus aureus distributed by the fingers to bilaterally symmetric areas of the skin, where seemingly a bacterial allergic state and chronic circumscribed lesions develop. This supposed focal cutaneous allergy is regarded as a constitutional dermatoneurotrophic reflex, similar in mechanism to that in neurodermatitis and atopic dermatitis, inducing regional lowered resistance and a consequent delayed response to therapy.

This dermatosis was described by Adamson [1] in 1908 as "a form of chronic superficial dermatitis in circumscribed patches with symmetrical distribution occurring in children"; he referred to the circumscribed patchy character of the eruption, the dry adherent crusting and scanty exudate, its probable pyococcic origin and its resistance to treatment. Adamson expressed the belief that most dermatologists at the time regarded it as a dry circumscribed discoid eczema.

Chronic symmetric impetigo is seen most frequently in children and young adults, but may occur at any age, and is divided about equally between the sexes. It may continue as an eruption for months or years, is very refractory to treatment and may recur after having apparently disappeared for weeks or months, but freedom eventually ensues when the skin has regained its normal physiologic resistance.

While this resistant and recurrent orbicular impetigo is usually sparse, it may be diffuse and involve large symmetric regions of the skin. Some patients complain of almost no subjective sensations, especially children, while others are annoyed by the constant tingling and pricking sensations in the lesions. Scratch marks and excoriations are usually absent, but some adult patients actually excoriate the lesions, causing bleeding and temporary disfigurement. The

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From the Dermatologic Department, Pittsburgh Children's Hospital, Pittsburgh.

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Canada, June 5, 1947.

1. Adamson, H. G.: On a Form of Chronic Superficial Dermatitis in Circumscribed Patches with Symmetrical Distribution Occurring in Children, Brit. J. Dermat. **20**:109 (April) 1908.

majority of patients present a mild and sparse eruption limited, for example, to the deltoid regions and extensor surfaces of the forearms; or to the shoulders, outer aspects of the arms and legs, or to the thighs, tibial regions and ankles, usually without evidences of scratching or excoriation.

Though the general texture of the skin is often normal, it is usually xerodermic or even mildly ichthyotic, a feature considered of intrinsic significance in diminishing the normal defensive properties of the skin, rendering it more susceptible to surface staphylococcic infection and lowering of resistance.

Chronic symmetric impetigo commences as minute normal skin-colored papules or papuloid lesions of a rather conical shape, ranging in size from that of a pinpoint to that of a pinhead (0.5 to 2.0 mm.). These papule-like lesions, or pseudopapules, are not true papules, but are localized edematous epidermal reactions about a minute vesicle the contents of which have dried into a small adherent globular crust. These papuloid lesions tend to form in groups which in the early stages may consist of only two or three papules separated by a few millimeters of normal skin, but soon these increase in number to a dozen or more. Removal of the small crust of these early papular lesions reveals a tiny dell or pitlike depression, from which exudes a minute amount of clear or pale straw-colored serum which on culturing gives a pure growth of hemolytic Staph. aureus. The scanty serous exudate from each papule dries promptly into another small adherent pale yellow beadlike crust.

The initial papules, or pseudopapules, disappear as the lesion develops into a rounded or ovoid circumscribed patch of dermatitis with a dry adherent shallow crust of either a gritty consistency and grayish white or of a larger granular consistency and pale yellowish with a crinkled appearance. They do not show the exudative feature of impetigo contagiosa. Forcible removal of the crusting may reveal an underlying small cribiform pitting, signifying that the crusts consist of an aggregation of minute dried vesicles. Occasionally the crusting is so thin as to be almost scalelike. The base of the patch is either pinkish or yellowish red or rosy red, and the redness if often increased at the periphery which may show a narrow rimlike ring of disorganized corneous cells. Sometimes the lesional base is of normal skin hue. The patches range from a few millimeters to several centimeters in diameter, and, while they are variously sized, some small and others large, they average 1 to 4 cm. in diameter and are often all of the same relative size. Satellite papules may develop into another patch,

which may remain discrete or enlarge and merge into the larger lesion, resulting in patches many centimeters in diameter.

When the early papular lesions or the later circumscribed patches are rubbed vigorously, as with an ointment, they may show a peculiar blanching, similar to that seen in Sergent's white line dermographia. This paling reaction is limited in the early phases to the conical papules, while in the patchy phase it occurs throughout the rubbed region. This friction made pallor subsides in less than one minute but often brings on a tingling itchiness which may constitute the chief complaint of many of the older patients with chronic symmetric impetigo and from which relief may be primarily sought.

The patches of chronic symmetric impetigo are often orbicular, and the average case shows a multiplicity of this type of lesion. The patches develop bilaterally in almost diametrically opposite regions of the skin, a symmetry of distribution which occurs regardless of the number of patches. They must be well developed on one side, while the opposite region may show either the early papular lesions or smaller circumscribed patches. Occasionally a few lesions may be regionally unilateral. Satellite papules of small orbicular lesions on one side are often found developing in the same relative position to a patch on the opposite side. This manifest and striking distributional symmetry of patches is attributed to a bilateral regional susceptibility caused by some sensitizing neurotrophic mechanism in the skin, probably a systematized bacterial allergy.

While only two or three bilaterally symmetric regions are involved in the majority of patients, almost any number of opposing regions may be involved symmetrically. In the sparse type of eruption the patches occur most frequently on the extensor surfaces of the extremities. They occur less frequently on the flexor surfaces of the arms and legs and occasionally in the flexures of the elbows and knees. In the more pronounced type of eruption many patches may be scattered diffusely on the face, trunk and the extremities, each in striking symmetry. In the profuse type of eruption, complicated by more pronounced inflammatory reaction with some serous exudation and increased crusting, the coalescence of patches may result in large areas of involvement on the arms or/and legs resembling infectious eczematoid dermatitis. Satellite patches may occur on the face, trunk and dorsal surfaces of the hands and feet. This type is due to an overgrowth or superimposed infection with Staphylococcus pyogenes aureus and Staphylococcus albus on chronic symmetric impetigo. The characteristic bilateral symmetry is retained in this profuse type in the delineational outline of the eruption even to bizarre extensions of the process or as uninvolved indentations or enclosures of normal skin.

BACTERIOLOGIC OBSERVATIONS

Careful culture of the scanty serous exudate of the early papular lesions after the minute adherent crust has been removed shows on blood agar mediums the growth and hemolytic action of Staph. aureus hemolyticus, which is evidently the primary cause of chronic symmetric impetigo. The hemolytic Staph. albus may play a causative role in some cases. Cultures from the crusts show an abundance of Staph. aureus and/or albus but by repeated culture the hemolytic Staph. aureus can be recovered. In searching for hemolytic staphylococci it is often necessary to make several cultures. The hemolysis reaction in blood agar is sometimes complete as a narrow zone about the culture colony in some cases, while in others it is broad, partial and hazy.

Coagulase tests in blood plasma for determining pathogenicity was done with many cultures and showed either a positive or a negative reaction, but this seemed to have no direct relationship to the mildness or the severity of the cutaneous lesions of chronic symmetric impetigo. The streptococcus evidently plays no role in the pathogenesis of the eruption. Out of a total of 86 cases the hemolytic Staph. aureus was recovered in 70 (about 81.4 per cent).

MICROSCOPIC APPEARANCE

Microscopic study of tissue was done in only a few instances, as it was felt that the character of the lesion did not warrant tissue removal. The epidermis showed a slight widening with normal rete prolongations. Intracellular and intercellular edema occurred in the upper levels of the rete mucosum with cellular disorganization near the surface, where keratin cells were lifted up and disorganized about a shallow mass of edematous cells surrounded by an inflammatory exudate of polymorphonuclear leukocytes and epithelial cell debris. Polymorphonuclear leukocytes were scattered among the rete cells at all levels. The granular cells were normal in some areas and disorganized or absent in others. The papillary body of the corium showed a mild perivascular polymorphonuclear leukocyte exudate with no alteration in the blood vessels or the collagen fibers. There was a moderate scattering of polymorphonuclear leukocytes in the upper part of the corium.

DIFFERENTIAL DIAGNOSIS

There is no particular difficulty in diagnosing chronic symmetric impetigo when one notes the characteristically circumscribed, often orbicular, nonexudative patches of yellowish, pinkish or rosy red, covered with either an adherent scalelike or a gritty granular yellowish crust and located with striking bilateral symmetry on the extensor

surfaces of the extremities and the trunk and occasionally on the flexural surfaces of the extremities and the face. The patches are without subjective sensations in children, whereas in the adult they may be itchy. The first impression is frequently that they are impetiginous, especially when superinfected with Staph. pyogenes aureus, but when the surface of the patches has a dry scalelike or a shallow granular yellowish crusting the possibilities of other dermatoses must be considered. The dermatoses to be differentiated in the diagnosis of chronic symmetric impetigo are impetigo contagiosa, impetigo pityroides, infectious eczematoid dermatitis, impetiginized nummular eczema, atopic dermatitis, contact dermatitis, seborrheic dermatitis, trichophytosis corporis and parapsoriasis en plaque, each of which will be described briefly for comparison.

Impetigo contagiosa is an acute exudative inflammation due primarily to the streptococcus, a serogenic rather than a pyogenic micro-organism, extending subcorneously. The staphylococcus grows secondarily and abundantly in the profuse serous exudate, forming piled up amber crusts in irregularly outlined areas of asymetric distribution usually on exposed surfaces. The solely staphylogenic impetigo does not show the dripping serous exudation of impetigo contagiosa.

Impetigo pityroides is a subacute nonexudative and noninflammatory streptogenic dermatosis entirely supracorneous forming circumscribed ovoid patches with a thin adherent grayish powdery or scalelike crust which does not pile up. The patches occur on the face, neck and upper extremities of children and are distributed irregularly without bilateral symmetry. Thus these three types of impetigo differ considerably in their clinical features from chronic symmetric impetigo.

Infectious eczematoid dermatitis is an irregularly patchy or diffuse asymmetric staphylogenic infection of the face, trunk or extremities which is usually a secondary surface extension of an infection from a pyococcic focus, such as a furuncle or a purulent discharge. The involved areas show irregularly piled up yellowish crusts with an underlying exudative and inflammatory reaction, sometimes accompanied with local lymphangitis which may extend to regional lymph nodes. A diffuse extension of secondary staphylococcic superinfection on chronic symmetric impetigo may simulate infectious eczematoid dermatitis, but the delineational symmetry of involvement of the former is retained.

Eczema, a difficult entity per se in the adult, is a sterile diffuse or localized edematovesicular reaction in the epidermis to an endogenic agent, the eczemagen. Genuine eczema occurs in infancy as

an autosensitization to food protein. In the adult endogenous eczema can occur as an eczematid from autosensitization to a specific food or drug allergen or a by-product of diseased tissue (cholecystitis, prostatitis, focal infection, malignancy) circulating in the peripheral capillary network. Orbicular hemolytic staphylococcic impetigo may closely resemble nummular eczema.

Atopic dermatitis is the cutaneous manifestation of the eczema-asthma-ichthyosis syndrome in which all external and internal epithelial tissues are hereditarily xerotic and unable to cope normally with the contactant, inhalant and ingestant noxae to which the congenitally defective epithelium becomes sensitized. This dermatosis is primarily flexural, often with an erythematoneurodermatitic response, which in severe types may be exudative. Flexural chronic symmetric impetigo is pale red, dry, without lichenization and with a thin scale-like crust.

Contact dermatitis is a primarily erythematosquamous or erythematovesicular reaction to an extraneous irritant or allergen. The local edema and vesication may give an eczematous or eczematoid appearance and though the primary lesions are sterile the exudate often becomes secondarily infected with nonhemolytic staphylococci which form yellowish crusts. Occasionally the reaction may be papulovesicular or rather pseudopapulovesicular. Predisposing factors are xeroderma and prolonged physicochemical trauma (cold, sweat, alkalis). Exposed surfaces are usually involved and rarely with bilateral symmetry. Many cases of contact dermatitis clinically resemble chronic symmetric impetigo.

Seborrheic dermatitis is a subacute superficial yellowish pink greasy scaling patchy eruption, involving the middle vertical regions of the face and trunk and the middle flexural areas of the extremities. It is dependent on the seborrheic constitution which is expressed as a lowered skin tone, probably due to hypovitaminosis B and a low protein–high carbohydrate diet, which favors the growth of Pityrosporum. The lesions are symmetric in a vertical sense, whereas chronic symmetric impetigo is symmetric in a horizontal sense.

Trichophytosis corporis shows irregularly round or oval patches with a defined vesiculocrustaceous border and a faintly lichenized pinkish yellow surface, with a loose scaliness in which mycelia may be found or cultured. There is no symmetry to the eruption unless bilaterally flexural areas are involved.

Parapsoriasis en plaque is an eruption of variously shaped patches of pale red to brownish red, ranging in size from a few to several centimeters, level with the skin, without infiltration, nonexudative and with a fine adherent pityriasic scaliness which may be almost imper-

ceptible. There are no subjective sensations of tingling or itchiness and the eruption is decidedly chronic and resistant to treatment. The patches do not show the fine gritty or granular adherent crusts, nor are they disposed in the bilaterally symmetric manner of chronic symmetric impetigo, though in some cases the lesions closely resemble one another.

REPORT OF CASES

While the majority of cases were encountered in children between the ages of 5 and 12 years, a few were encountered in children as young as 1 year and in youth between 12 and 20 years of age. Among adults the patients were mostly between 20 and 35 years of age, while the oldest was 52 years.

The following brief reports of 10 cases will suffice to reveal the average features of chronic symmetric impetigo, in which the similarities of clinical observations and chronicity are evident.

CASE 1.—J. T., a girl 10 years of age, was seen in 1940 for an eruption of two and a half years' duration, consisting of sharply circumscribed, rounded, superficial, pinkish red, nonexudative, scaling and shallow crusting lesions, measuring 1 to 3 cm. in diameter. These were distributed bilaterally and symmetrically on the cheeks, outer aspects of the arms, scapular and lumbar areas, buttocks and extensor surfaces of the thighs and legs. She had received a variety of topical remedies without benefit. Culture from the lesions revealed hemolytic staph. aureus.

CASE 2.—E. S., a boy 9 years of age (fig. 1), was seen in 1941 because of nonexudative rounded circumscribed shallow crusted lesions with a pale reddish base, ranging from 1 to 4 cm. in diameter, which were scattered symmetrically over the extensor surfaces of both arms and forearms, the gluteal areas and the anterolateral and posterior surfaces of the thighs. These patches had been present eight months and had been treated by several physicians and in two dermatologic clinics, where such diagnoses as eczema, contact dermatitis and seborrheic dermatitis had been made. Cultural studies showed hemolytic Staph. aureus.

CASE 3.—J. F., a girl 8 years of age (fig. 2 *A*), was seen in 1942 because of many thickly crusted cutaneous lesions of rounded or irregular shape, varying from 6 to 12 cm. in diameter. The eruption was of three years' duration and was distributed bilaterally on the elbows and knees, buttocks and femorogluteal folds, external and posterior surfaces of the thighs, the popliteal areas and on each ankle just above the external malleolus. During this time they had not responded to various types of treatment. Repeated culturing from the lesions finally disclosed hemolytic Staph. aureus.

CASE 4.—H. F., a boy 8 years of age with a mildly ichthyotic skin, was seen in 1944 for an eruption of one and a half years' duration, consisting of rounded superficial dry pale yellowish crusted lesions ranging from 6 to 8 cm. in width and distributed bilaterally on each elbow tip and the adjacent extensor surfaces of the arms and forearms, the middle portion of the extensor surface of each thigh and the posteroexternal surface of each leg below the calf. These lesions had received considerable local treatment, with improvement on several occasions. Culture of the lesions disclosed hemolytic Staph. aureus.

CASE 5.—J. K., a boy 5 years of age (fig. 2 *B*) with a xerodermic skin, was seen in 1943 for an eruption of nonexudative rounded shallow crusted pinkish red lesions measuring 5 to 7 cm. in diameter. These patches were distributed bilaterally and symmetrically on the scapular areas, the middle and lower parts of the back, the lateral surfaces of the trunk, the hips and buttocks, the middle portion of the posterior surfaces of the thighs, the outer aspect of each leg above the ankle and

Fig. 1 (case 2, E. S., aged 9 years).—Dry granular crusted small circumscribed patches involving the buttocks and thighs bilaterally and relatively symmetrically.

in the flexures of the elbows and knees. The lesions were of eight months' duration and were not itchy. Cultures from all of the lesions showed hemolytic Staph. aureus.

CASE 6.—B. R., an unmarried woman 21 years of age, was seen in 1938 because of superficial, rounded, faintly erythematous, finely granular, crusted, nonexudative and slightly itching lesions ranging from 3 to 6 cm. in diameter. These patches had been present two years and were distributed bilaterally and symmetrically on

the outer surfaces of the arms, the extensor surfaces of the forearms and the lower laterodorsal surfaces of the trunk. Culture revealed hemolytic Staph. aureus and hemolytic Staph. albus.

CASE 7.—J. A., a man 23 years of age, was seen in 1946 for a chronic erythematocrusteaceous dermatitis involving both upper extremities from the wrists to the shoulders. The lesions began eight months previously as circumscribed rounded yellowish crusted patches on the outer surfaces of both arms and the extensor surfaces of both forearms in symmetric locations. These patches had resisted local treatment of various kinds, and during these eight months new lesions had developed in symmetrically adjacent areas which enlarged and coalesced with the older ones until the entire surface of the skin of both upper extremities was involved from the wrists to the shoulders. There was no history of any other pyococcic pro-

Fig. 2.—*A* (case 3, J. F., aged 8 years), relative symmetry of distribution of circumscribed patches with a superinfection of Staph. aureus. *B* (case 5, F. K., aged 5 years), superficial circumscribed patches involving symmetric regions bilaterally on the trunk and extremities.

cess previous to the onset of the patchy circumscribed eruption. Culture disclosed a profuse Staph. aureus growth, but repeated culture finally revealed hemolytic Staph. aureus. Though a diagnosis of infectious eczematoid dermatitis was applicable, the condition was considered chronic symmetric impetigo complicated by a profuse superimposed staphylococcic overgrowth from the early history of the eruption and the delineational symmetry of involvement.

CASE 8.—M. T., a man 28 years of age, was seen in 1945 because of itching grouped small almost normal-skin-colored papule-like lesions located bilaterally on the arms over the deltoid muscle insertion, the proximal extensor surfaces of the forearms and the outer surfaces of the thighs, legs and ankles. These lesions, really pseudopapules, had been recurring in these areas for two and a half years, and

their itchiness was his chief complaint, which amounted almost to a neurosis. There was no itching during the periods of intermittence. Each papule was capped with a tiny adherent yellowish beadlike crust, which on removal left a minute pitlike depression and exuded a small drop of clear serum, from which a pure culture of hemolytic Staph. aureus was obtained. These lesions showed a paling reaction on rubbing. Though the eruption had been regarded as a possible contact dermatitis, no external irritant could be discovered. A diagnosis of chronic symmetric impetigo was made, which disappeared with topical antibacterial remedies.

CASE 9.—C. Z., a married woman 34 years of age, was seen in 1947 for an eruption of five and a half years' duration, consisting of superficial pale reddish patches measuring 1 to 4 cm. in diameter on the dorsal and external surfaces of the feet, the inner surfaces of the ankles, the lower portions of the anterior and posterior surfaces of the legs and the middle third of the anterior surfaces of the thighs. These lesions, distributed bilaterally and symmetrically, were rounded,

Fig. 3 (case 10, W. A., aged 52 years).—Bilateral symmetric patches on the ulnar surfaces of the forearms (*A*) and the tibial surfaces of the legs (*B*). Cribiform pitting and excoriations are evident on the left leg.

ovoid or irregular in shape, were both discrete and confluent and had a thin scalelike covering suggestive of a contact lacquer dermatitis (nail lacquer had never been used). The patches were moderately itchy. Culture showed hemolytic Staph. aureus; the dermatitis disappeared with antibacterial applications.

CASE 10.—W. A., a man 52 years of age (fig. 3), who had chronic myocarditis, was seen in 1939 for an itching nonexudative superficial shallow yellowish crusted lesion with a dull erythematous base, measuring 5 cm. in diameter, on the middle inner portion of the flexor surface of each forearm, of three and a half years' duration. Both anterior tibial surfaces of the legs showed similar, but larger, lesions, measuring 8 by 18 cm. in diameter and of three years' duration. These symmetrically bilateral lesions had never completely disappeared under treatment but showed repeated recrudescences. Various diagnoses had been made of his intractable condition. Culture revealed hemolytic Staph. aureus; the lesions responded favorably after several weeks of treatment.

TREATMENT

There is no single method of treatment that is satisfactory in all cases of chronic symmetric impetigo. One form of therapy will benefit some and be of no help to others. Antiseptic solutions, such as 3 per cent boric acid solution, 1 per cent aluminum acetate solution or 1 : 5,000 potassium permanganate solution, used periodically as wet dressings, are useful. Topical antibacterial ointments are of value in most cases. Antibiotic ointments are useful at times, but are occasionally disappointing. Penicillin therapy may be effective in some cases. Staphylococcus toxoid injections have been disappointing. Ultraviolet irradiation in conjunction with an antibacterial ointment is frequently efficacious. Roentgenotherapy is of doubtful value.

Sparsely scattered lesions often respond favorably to the local application of a 1 to 5 per cent aqueous solution of silver nitrate, 1 per cent aqueous solution of methylrosaniline, 1 per cent solution of coal tar in acetone or 0.1 per cent aqueous solution of potassium permanganate. Antibacterial ointments applied with gentle friction are effective and may be used in varying strengths. Irritation may be avoided if they are not too strong and their application is not too frequent or prolonged. The most useful are 1 per cent strengths of either ammoniated mercury, yellow mercuric oxide, chrysarobin or salicylic acid, or 0.25 per cent strengths of crude coal tar, "quinolor compound ointment" (contains 10 per cent benzoyl peroxide and 0.5 per cent "quinolor [a mixture of three chlorine derivatives of 8-hydroxyquinoline] in a base of equal parts of petrolatum and wool fat) or nitrofurazone. When changing from one antibacterial agent to another it is often advisable to have an interval of two or three days' treatment with boric acid ointment alone. Irritation of the lesions is to be avoided. The general application of simple creams to promote softness, lessen dryness and increase the physiologic lubricity of the skin is sometimes of more value than a possibly irritating antibacterial agent.

Medication of a dermatotonic nature, such as cod liver oil, vitamin A or injections of crude liver extract, may be beneficial.

CONCLUSIONS

Chronic symmetric impetigo is a not infrequently occurring infection on the skin of the face, trunk and extremities, evidently caused by the hemolytic Staphylococcus aureus. This organism is distributed by the fingers to symmetrically bilateral regions, in which a systematized bacterial allergy seemingly develops. Mild or pronounced xeroderma furthers the lowering of resistance by lessening the normal defensive properties of the skin. The bacterial allergy mechanism

combined with dryness of the skin brings about a decided chronicity to the eruption, which consists of superficial, circumscribed, variously sized rounded, ovoid or irregularly outlined nonexudative adherently crusted patches, pinkish yellowish red or rosy red, which are remarkably intractable to treatment. The lesions are without subjective sensations in children, whereas in adults itching may be an annoying factor.

Chronic symmetric impetigo occurs most frequently in children and less frequently in adults and about equally in the two sexes. Chronic symmetric impetigo is often erroneously diagnosed as impetigo contagiosa, impetiginized eczema, nummular eczema, eczematoid dermatitis, seborrheic eczema, contact dermatitis, atopic dermatitis and occasionally as infectious eczematoid dermatitis.

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ABSTRACT OF DISCUSSION

Dr. Donald M. Pillsbury, Philadelphia: Like Dr. Crawford and, I am sure, many other dermatologists, my co-workers and I have been interested in this difficult disease complex, because the condition presents great resistance to treatment. We have also for some time been studying this and other eczematous eruptions from the bacteriologic point of view. We have studied at least a hundred such cases bacteriologically as carefully as we could.

Certainly we do not know the basic cause of the eruption, though there are many factors which may play a role in it. In this type of dermatitis the patient is often extremely sensitive to vaccines or toxoids of staphylococci. I think that one thing that we have learned is that skin which has had its integrity disturbed inevitably harbors staphylococci and streptococci, which may be pathogenic. I do not believe that one can accept the thesis that the cause of the eruption is primarily bacterial. There is a bacterial element, but if one used the same reasoning one would come to the same conclusion with many other chronic eruptions.

I do not believe that the term "chronic symmetric impetigo" is an acceptable one for this condition.

Dr. James R. Driver, Cleveland: This is a very interesting and valuable paper, for the author attempts to place in a special classification a group of cases about which little is known and in which the condition has been diagnosed as any one of several other diseases. This disease, which Dr. Crawford has named "chronic symmetric impetigo," is apparently not uncommon and has varying clinical manifestations. After reviewing Adamson's [1] original article, published nearly forty years ago, in which he describes a new disease under the title of "A Chronic Superficial Dermatitis in Circumscribed Patches with Symmetrical Distribution Occurring in Children," I am convinced that Dr. Crawford's cases are of the same type. It is indeed interesting that until the present time no mention of this entity is found in the literature, nor is it included in any of the standard textbooks of dermatology. Although Dr. Crawford states that there is no particular difficulty in diagnosing this disease, I think that it is fair to state that there would be a difference of opinion among many dermatologists concerning the diagnosis in any particular case that Dr. Crawford has reported as an example of this condition. Therefore, I suspect that he has anticipated some difficulty in securing the general acceptance of his concept that chronic symmetric impetigo is a definite disease entity caused by hemolytic Staph. aureus.

To me, the differential diagnosis between this disease and nummular eczema, infectious dermatitis, trichophytosis corporis, atopic dermatitis and seborrheic dermatitis, in many instances, could be extremely difficult from a clinical point of view. Adamson pointed out that there were other dermatoses most certainly of coccic origin which were indistinguishable clinically from this chronic symmetric circumscribed eruption. Furthermore, the question arises as to whether the hemolytic Staph. aureus plays a dominant or contributory role. We all know that this organism, along with many other pyogenic bacteria, may be cultured from similar eczematoid dermatoses and even from the normal skin of many persons. However, the observation of the hemolytic Staph. aureus in such a large percentage of the cases is in favor of its causative significance.

Dr. Crawford made no mention of the use of fungus cultures; yet, clinically, in some of the cases there is a resemblance to Trichophytosis corporis. I wonder whether, in the bacteriologic investigations, Dr. Crawford has employed the culturing on three successive tubes, as suggested by Lewandowsky and Sabouraud. This technic will often reveal that Streptococcus is also involved in the infection and that it may, in fact, be the predominant organism in some instances.

Diagnosis is further complicated because symmetry, oval or circumscribed lesions and chronicity are common to several of the diseases mentioned in differential diagnosis. While the disease is frequently mentioned as being nonexudative, crusting of one type or another is present in nearly all the cases. Crusts are usually considered as being evidence of exudation.

Dr. Crawford's explanation of the cause, distribution and chronicity as due to bacterial allergy and dermatoneurotrophic reflex, reveals a conscientious and careful study, for which he is to be commended.

Chronicity and intractability to therapy, which are characteristic features in so many of these cases, are probably due to interference with the factors of autogenous disinfection. This would be particularly true in those patients with mildly ichthyotic skin. I predict that Crawford's chronic symmetric impetigo, whether it is generally accepted as a disease entity or not, will be a frequent diagnosis among dermatologists in the future.

DR. STANLEY CRAWFORD: I wish to thank Dr. Driver and Dr. Pillsbury for their interesting discussions. The characteristic symmetry of the foci of the lesions is an important factor in this type of cutaneous infection, which is difficult to explain except on a basis of regional sensitization. No cultural studies for fungi were made from surface scrapings, but these were examined microscopically for mycelia and spores in many of the cases, and none were found. That the hemolytic Staphylococcus is the etiologic and sensitizing agent in chronic symmetric impetigo is not contended, but its frequent association and its being obtained in pure culture from the early lesion seem to indicate that it may be the causal organism. I feel that there is a variety of impetigo in which the lesions are orbicular and distributed symmetrically, chronic in their course and moderately resistant to therapeutic measures. I hope that others will interest themselves in this varietal type of impetigo which was so ably described by Adamson.

AUTOSENSITIZATION DERMATITIS

Report of Five Cases and Protocol of an Experiment

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THE CONCEPT of a person's becoming sensitized, in one or more of his organs, to a substance elaborated in or on his body from his own tissue proteins has intrigued many investigators.

Whitfield [1] was probably the first to apply this concept to the field of dermatology. He reported, in 1921, the cases of 2 patients in whom generalized toxic eruptions developed ten days after they had incurred large hematomas due to trauma. A generalized papular, urticarial rash developed in a third patient eleven days after an acute exacerbation of dermatitis of the legs. In another patient a red-streaked, urticarial wheal developed whenever serum from a vesiculobullous eczema of the legs came in contact with normal areas of the skin. For these interesting dermatologic phenomena Whitfield coined the term autosensitization.

In 1945, Smith [2] reported, under the name "eczema autolytica," the same type of autosensitization dermatitis as in Whitfield's third patient: Patients with chronic eczema of the legs, with or without ulceration, first experienced exacerbation of the local process, and then, in a week or two, generalized acute vesicular eruptions developed. Smith stated the belief that a dermolysin formed at the site of the primary eruption was the cause of the widespread dermatitis. He felt that this dermolysin might be a foreign protein of bacterial origin or, more likely, that it might be a product of the breakdown of tissue or a combination of the two.

In our opinion the cases of Dennie and others,[3] reported in 1929, belong in a broadened concept of Whitfield's autosensitization dermatitis. They noted generalized exfoliative dermatitis following local dermatitis around burned areas treated with trinitrophenol and expressed the opinion that the generalized dermal reaction was due to a sensitization

1. Whitfield, A.: Some Points in the Aetiology of Skin Diseases (Lumleian Lectures), Lancet **2**:122 (July 16) 1921.

2. Smith, S. W.: Eczema Autolytica, Brit. M. J. **1**:628 (May 5) 1945.

3. Dennie, C. C.; McBride, W. L., and Davis, P. E.: Toxic Reactions Produced by the Application of Trinitrophenol (Picric Acid), Arch. Dermat. & Syph. **20**:698 (Nov.) 1929.

to "protein picrinate" elaborated at the site of the burn and carried by the blood stream.

Hopkins and Burky [4] reviewed the various "ids," pointing out that they are phenomena of autosensitization, and stated the belief that many eczemas of the hands are due to sensitization to a combination of the patient's own keratin and staphylococcus toxin. In support of this theory, they reported good clinical results following desensitization with staphylococcus toxin.

The clinical diagnosis of autosensitization dermatitis and the pathogenic mechanism as postulated by Whitfield and others have proved to be extremely practical. Knowledge of the chain of events has helped us to understand a great many examples of severe, widespread dermatitis in our practice.

TYPES OF AUTOSENSITIZATION

The types, with comment on the mechanisms involved, are reviewed.

Autosensitization Due to Absorption of the Patient's Blood.—This is the purer form and the rarer. Whitfield observed it in 2 patients with large hematomas. It is possible that some of the rare toxic eruptions of the menstrual period may belong in this classification. Also, the postpartum toxic erythemas and erythema multiforme might, at least theoretically, be explained on the basis of autosensitization to altered lochial discharges absorbed from the uterus or vagina.

Autosensitization and Widespread Dermatitis Following Exacerbation of Local Dermatitis.—This, the commoner variety, was that observed in Whitfield's third patient and in Smith's patients with "eczema autolytica." As many of these patients have been observed through the years, a clearcut, composite picture has evolved. The typical patient is an elderly woman who gives a history of eczema of the legs for many months or years. Often she will have had ulcers of the legs with the eczema. Suddenly, under the influence of trauma, heightened activity of the patient (accompanied with increased edema), injudicious self treatment or secondary infection, there occurs a sharp exacerbation of the lesions, with extension at the periphery of the eruption. Then, in ten days or less, patchy areas of macular, papular, vesicular or urticarial dermatitis appear on the opposite leg and on the thighs, forearms, arms, face, neck and trunk. If proper treatment is not instituted the acute, generalized process persists or becomes severer, but if the patient is put to bed with the legs elevated and in damp dressings the generalized eruption subsides synchronously with or shortly after the improvement of the eczema on the legs.

4. Hopkins, H. H., and Burky, E. L.: Cutaneous Autosensitization: Role of Staphylococci in Chronic Eczema of Hands, Arch. Dermat. & Syph. **49**:124 (Feb.) 1944.

This sequence of factors (the existence of a local eruption, from which absorption could take place; the explosive, generalized, symmetric, toxic eruption; the classic time interval of eight to ten days, and the subsidence of the generalized process concurrently with improvement of the local process) leaves little doubt that one is dealing with a phenomenon of sensitization. But one can, so far, only theorize as to the nature of the antigen involved. Possibly this antigen consists only of the patient's own altered tissue protein. We are inclined to believe that this is true in some cases, for we have seen the syndrome occur when there was very little evidence of local infection and no history of the local application of drugs. It is also possible that the antigen originates in bacterial infection of the eczema on the leg or as a conjugation of bacteria and tissue protein. But in our opinion the antigen in the greatest number of cases is a drug-protein combination, such as the "protein picrinate" described by Dennie, for many exacerbations occur after local application of some potentially irritating substance, such as a preparation of iodine or mercury or a patent liniment. During the war we saw several cases in which such episodes occurred after treatment of burns with ointments containing sulfonamide drugs or butamben (butesin®) picrate, and more recently exacerbations have occurred after the local application of penicillin.

This syndrome is, of course, not limited to patients with eczema of the legs. It may occur after any severe localized dermatitis, be it bacterial, mycotic, chemical, thermal, actinic or idiopathic in origin.

THEORY OF MECHANISM

The idea that persons or experimental animals could be artificially sensitized or could become spontaneously sensitized to proteins from their own bodies or from those of other persons or animals has interested many investigators. It has been definitely established that rabbits can be sensitized to their own lens tissue or muscle tissue by inoculation with a mixture of such tissues and staphylococcus toxin. After such sensitization the lenses become highly sensitive to nonspecific stimuli; needling of the lenses produces explosive local reactions far greater than occur when normal rabbit lenses are needled. Human beings have been experimentally sensitized to human blood, serum and skin. Bizzozero [5] reported that he had been able to sensitize human subjects to their own serum and blood with intradermal injections of these substances. When, at a later date, the same substances were injected into or near the original sites of injections, papules or urticarial reactions were produced. The papules showed a tuberculoid structure on micro-

5. Bizzozero, E.: Ueber die Sensibilisierung der Haut gegen das Eigenserum und das Eigenblut, Arch. f. Dermat. u. Syph. **173**:342, 1936.

scopic examination. In all such experiments the sensitization was organ specific rather than species specific. Several investigators pointed out that it is necessary to combine some substance such as bacterial toxins with the organ extract. When so combined the two act antigenically to produce sensitization, but they do not produce sensitization when used separately; this is important to remember when one is studying autosensitization in the human subject. Landsteiner and Jacobs [6] reported that simple chemical compounds (acyl chlorides) would produce sensitization in guinea pigs but that addition of guinea pig serum to the simple chemicals would produce a far greater degree of cutaneous sensitization.

Those who wish to study the subject further can find an excellent summary and bibliography in Sulzberger's text, "Dermatologic Allergy."[7] No better summary of the relation of experimental evidence to the actual occurrence of autosensitization dermatitis could be made than his:

> Is it not possible that damage to the skin—alteration and liberation of skin-constituents (either through infection or through physical agents or through reactions to allergens)—may create and liberate skin antigens which, in turn, produce skin specific antibodies which, in turn, produce reactions in the skin itself, wherever and whenever skin antigen is made available and accessible to their action? Would not this hypothesis explain—perhaps better than all others—the recognized fact that after an eczematous response has been produced in one area, there often follow months and years during which, not only the areas of exposure, but also almost all other skin sites, react with pathologic responses to all manner of forces and substances previously innocuous and previously tolerated?

To carry this reasonable theory over to the problem of autosensitization dermatitis, a sequence of events may be postulated: Because of absorption from an old eczema of the leg of her own tissue protein products, unaltered or combined with local bacterial toxins or with medicaments, a patient acquires circulating antibodies in her blood stream. These antibodies become attached to remote areas of skin and an antigen-antibody reaction, dermatitic in nature, results. Selection of the sites of dermal reaction may be conditioned by local external irritation analogous to the experimental needling of a sensitized rabbit lens.

INFECTIOUS ECZEMATOID DERMATITIS

What is the relation of infectious eczematoid dermatitis to autosensitization? Engman's description of infectious eczematoid dermatitis as beginning at or around a site of pyogenic infection and spreading by peripheral extension or autoinoculation to remote areas was obviously

6. Landsteiner, K., and Jacobs, J.: Studies on the Sensitization of Animals with Simple Chemical Compounds, J. Exper. Med. **64**:625 (Oct.) 1936.

7. Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C Thomas, Publisher, 1940, pp. 415-432.

the concept of direct bacterial cutaneous infection.[8] However, Sutton[9] noted that in some cases the dermatitis began as described by Engman and that generalized urticaria (which he regarded as an allergic reaction to the products of the original dermatitis) developed later. Such cases can probably be classified as instances of autosensitization.

The work of Hopkins and Burky[4] and others, showing that sensitization can develop to a combination of tissues and bacterial toxins, may well explain the mechanism of infectious eczematoid dermatitis. The skin about a draining sinus becomes sensitized to the discharge containing both bacterial toxins and tissue products; this accounts for the local spread of the eruption. Humoral dissemination of the combined antigen may then result in a distant or generalized reaction.

It is probably true that many cases of nummular eczema are samples of local dermal, bacterial sensitization of this type and could be considered a variety of infectious eczematoid dermatitis. This may also be true of many of the eczemas of the external auditory canals and the retroauricular area.

If infection is a factor in seborrheic dermatitis, the various manifestations of this disease may represent another variety of infectious eczematoid dermatitis or, perhaps, a local autosensitization reaction in which the skin becomes sensitive to a combination of some fraction of itself and the products of various organisms of the scalp, such as Pityrosporon of Malassez. We have seen patients with seborrheic dermatitis of the scalp which has flared locally, after which a generalized "id" or autosensitization reaction has developed.

Local bacterial infection of the skin, the phenomena of the bacterids, infectious eczematoid dermatitis and autosensitization reaction in which bacterial products play a part may combine in many different ways to produce a great variety of cutaneous lesions.

TREATMENT

The treatment of autosensitization dermatitis depends on control of the original antigen-producing area of dermatitis and on desensitization of the whole organism.

The area of primary dermatitis must be kept at rest. In most instances this means keeping the patient in bed, with the leg elevated. Constantly applied wet gauze dressings with solution of boric acid, solution of aluminum acetate or plain water act to remove the exudate of the tissues (antigen). The lowered temperature which they produce is pleasing to the patient and reduces inflammation.

8. Engman, M.: Infectious Eczematoid Dermatitis, Am. Med. **4**:769, 1902.
9. Sutton, R. L.: Infectious Eczematoid Dermatitis, J. A. M. A. **75**:976 (Oct. 9) 1920.

Desensitization may be attempted by the time-proved method of intramuscular inoculation twice a week with 20 cc. of the patient's own blood. Newer methods of more specific desensitization, such as injections of staphylococcus toxin, as suggested by Hopkins and Burky, or of staphylococcus toxin combined with the patient's serum, may be tried. We suggest trial inoculation with a mixture of the patient's own serum and any drug which was being applied locally at the time of exacerbation of the original process. However, improvement usually occurs promptly on withdrawal of the drug and on the institution of soothing local treatment. It is our opinion that oral administration of tripelennamine hydrochloride (pyribenzamine hydrochloride®) and of diphenhydramine hydrochloride (benadryl hydrochloride®) have been of value.

REPORT OF CASES

CASE 1.—G. F., a 69 year old white woman, was seen on Nov. 24, 1946 with a subacute eczema on the lateral surface of the left leg. She had had phlebitis of the left leg and thigh forty years before, after childbirth, and had had ulcers on the ankle due to stasis on two or three occasions. There were varicose veins in the leg and thigh and pronounced edema in the ankle and leg, but no ulcers at the time of examination. The right leg was also edematous and showed a large patch of brawny infiltration and pigmentation above the ankle, but no eczematization was present.

The patient was advised to rest, lying down, except for short periods of necessary activity, for which support with an elastic bandage was prescribed. A lotion containing solution of coal tar (2 per cent), zinc oxide, starch, glycerin and calcium hydroxide solution was prescribed. The patient was much improved a week later.

On December 30 the eruption was much worse, with increased edema, erosion and weeping on the left leg. There was also a maculopapular eruption on the right leg and distributed symmetrically over the arms, shoulders and back. The patient had used no other medicines but had not been in bed. She had been on her feet more than usual, and the swelling had become progressively worse.

Results of patch tests and scratch tests with serum from the eroded, eczematous area on the left leg, performed on areas of normal skin at the height of the autosensitization reaction, were negative.

The eruption on the leg improved rapidly with bed rest and continuous cool, wet dressings with dilute solution of aluminum acetate. This was followed by clearing of the autosensitization reaction. The patient subsequently applied the lotion containing solution of coal tar without irritation.

CASE 2.—L. S., a 58 year old white man, was first seen on Sept. 30, 1946. He presented a chronic, infiltrated and scaling eczema of the feet, ankles and legs, which had been present for over a year. There was pronounced pitting edema secondary to varicose veins. He also showed a milder eczematization on the arms and on the back and sides of the neck, with a few scattered similar areas on the thighs and trunk. This widespread eruption had come on during the preceding three or four months and had flared during periods of increased swelling, redness, weeping and erosion of the eruption on the ankles and legs. Treatment had been relatively ineffective except for six weeks of hospitalization, during which the eruption had largely cleared.

Bed rest and application of wet dressings with dilute solution of aluminum acetate to the severer areas and of a bland lotion were advised. The patient was not seen subsequently until March 1947, at which time the eruption was more pronounced. There were severe edema, erosion and weeping of the eruption on the legs and ankles. The eczematization on the neck, arms and thighs was further developed and in large areas had become confluent, moist and crusted. The patient was hospitalized, and bed rest and bland local medication were ordered. The blood count, urine and dextrose tolerance were normal. Results of patch tests with medicaments previously used, shoe leathers and articles of clothing were negative. The patient improved slowly.

Serum from the eroded and weeping areas on his legs was applied to areas of normal skin in patch and scratch tests, but no reactions occurred. Likewise, the serum diluted with an approximately equal amount of isotonic solution of sodium chloride and passed through a Seitz filter produced no reaction when injected intradermally.

CASE 3.—K. C. B., a 48 year old white man, had had an episode of dermatitis of short duration on the left ankle about a year before he was first examined. He had had varicose veins for a number of years, and swelling of the ankles had been noted after periods of increased activity. The dermatitis recurred in the original area on the left ankle about Jan. 1, 1947. The eruption gradually became more severe, and more extensive, and about January 15 it appeared on the right leg and then on the arms, face, neck and (sparsely) on the trunk.

At this time the left leg was greatly swollen, and the skin was acutely inflamed, eroded and weeping profusely. No medication had been applied since the first recurrence.

Further physical examination and routine laboratory studies were noncontributory. Patch and scratch tests with serum from the leg produced no reactions. Serum collected from the leg, diluted with an approximately equal amount of isotonic solution of sodium chloride and passed through a Seitz filter produced no reaction on intradermal injection.

The autosensitization reaction cleared promptly with bed rest and bland local medication. The dermatitis on the left leg and ankle cleared more slowly.

CASE 4.—W. P., a 65 year old white man, was seen first on Oct. 21, 1946. He had burned the top of his left foot in February; it had been treated with a variety of medicines but had not healed. Instead, a dermatitis had developed, which involved most of the top of the foot. The condition had improved recently, however, and until nine days before he was first examined it had almost cleared. At that time a "red liquid medicine" had been applied. After this the dermatitis on the foot had flared acutely, and during the two or three days before he was first seen an erythematous, papulovesicular eruption had developed on his face, neck and arms. Results of patch and scratch tests with serum from the acute lesions of dermatitis on the foot were negative.

The dermatitis subsided under soothing local medication, and the patient was dismissed as well on November 19.

He was seen again on Feb. 6, 1947. He stated that one week previously a barber had shaved the left side of his neck too closely, causing a superficial abrasion. He had painted this once with tincture of merthiolate, and an acute dermatitis had rapidly developed on the left side of the neck and on the top of the shoulder. This was followed in less than twenty-four hours by the appearance of an eruption on the face, neck, shoulders and arms. At the same time there was a mild flare at the site of the dermatitis on the left foot.

Serum was collected from the weeping area on the left side of the neck. Results of patch and scratch tests with the serum were negative. The serum, diluted with an approximately equal amount of isotonic solution of sodium chloride, was filtered and injected intradermally, with no resulting reaction.

Patch tests made subsequently proved the patient's skin to be strongly sensitive to merthiolate.

The eruption cleared satisfactorily with bland local medication.

CASE 5.—L. G., a 29 year old white man, was seen in 1942 with a vesiculopustular dermatitis of the left great toe and a pustular folliculitis of the beard. The folliculitis cleared easily under local medication, but the dermatitis of the toe was slow to respond. Microscopic examination failed to reveal fungi, and culture showed a hemolytic staphylococcus. During the course of treatment for the eruption on the toe a maculopapular, erythematous eruption developed symmetrically on the neck and the upper part of the back. The patient disappeared from observation before the eruption was cleared.

He returned on Jan. 14, 1947 with a vesiculopustular eruption of the soles and sides of the feet. Repeated microscopic examination and cultures failed to reveal fungi. A culture made from the lesions showed hemolytic Staphylococcus aureus.

The eruption of the feet proved to be exceedingly resistant to treatment. Early in February an "id" type of dermatitis developed on the hands and face. At this time, both patch and scratch tests with serum from the weeping areas on the feet caused no reaction on the patient's skin. The dermatitis subsided rather quickly on the face but has persisted on the feet and hands to the time of writing.

A vaccine made from the hemolytic Staph. aureus cultured from the lesions on the feet was administered. This produced a pronounced local reaction in the skin, and when the dose was increased it caused a focal flare-up on both the hands and the feet.

CONCLUSIONS

In cases 1, 2 and 3 there was no evidence that infection or sensitivity to drugs played a significant part. The original dermatitis appeared to be primarily due to the damaging effects of circulatory stasis and edema.

In case 4 sensitivity to drugs appeared to be clearly responsible for the primary dermatitis.

In case 5 the primary dermatitis was bacterial in origin.

We were unable to demonstrate sensitivity of the patients' skin to serum from the primary dermatitis, as had been done previously by Whitfield and others. We have no adequate explanation for this.

EXPERIMENT IN SENSITIZATION TO HUMAN SKIN

A piece of normal skin approximately 1 by 4 inches (2.5 by 10 cm.) was removed at operation from a healthy white man. The skin was finely ground, further macerated in a mortar and extracted for twenty-four hours in a fluid consisting of sodium chloride, 5 Gm.; sodium bicarbonate, 2.75 Gm.; phenol, 4 cc., and sufficient distilled water to make 1,000 cc. The preparation was then filtered, first through a Büchner funnel and then through a Seitz filter. Eighty cubic centimeters of

fluid resulted. This was concentrated to 30 cc. through a cellophane membrane over silica gel, and the resulting clear, slightly amber-tinted fluid was used as an antigen.[10]

Blood was taken from 5 healthy adults, 3 women and 2 men. Serum was prepared and tested for precipitins with the skin antigen. The results are shown in table 1.

The antigen was then administered to 5 test subjects. Intradermal injections of 0.05 cc. of a 1 : 10 dilution of the antigen produced no immediate reaction. However, delayed maculopapular reactions, with an average diameter of 1 cm., appeared in

TABLE 1.—*Reactions to Precipitin Before Administration of Antigen*

	Antigen	
Patient	1:100 Dilution	1:1,000 Dilution
M. K.	+	±
J. H.	±	±
A. L.	±	±
H. A.	+	±
C. L.	±	±

all 5 persons in two or three hours and reached a peak in twenty-four to thirty-six hours.

The first dose of the antigen was given to 3 subjects intradermally and to the rest subcutaneously. It was observed that a single injection of 0.05 cc. intradermally or of 0.15 cc. subcutaneously produced a moderate delayed local reaction; this dose was not exceeded. Four injections were given over a period of sixteen days.

In 2 subjects the antigen was given subcutaneously in a cream prepared by precipitating aluminum hydroxide from aluminum sulfate with ammonium hydrox-

TABLE 2.—*Reaction to Precipitin After Administration of Antigen*

	Antigen		Control (Extracting Fluid),
Patient	1:1,000 Dilution	1:2,000 Dilution	1:1,000 Dilution
M. K.	+++	++	±
J. H.	++	++	±
A. L.	++	++	±
H. A.	+++	++	±
C. L.	++	++	±

ide and washing the precipitate until it was nitrogen free. Each patient was given three injections: 0.1 cc. on the first day, 0.2 cc. on the second day and 0.2 cc. on the fourth day.

Blood was again drawn from all 5 subjects on the sixteenth day after the first administration of the antigen. Serum was again prepared and tested for precipitins with the antigen. The results are shown in table 2.

In M. K., J. H. and A. L. the simple antigen was used. In H. A. and C. L. the antigen was used in the cream containing aluminum hydroxide.

10. The antigen and the filtrates of autogenous serum used for intradermal tests in the cases presented were prepared by Dr. Albert Rowe, of Oakland, Calif.

Dr. Gertrude Moore, of the Western Laboratories, Oakland, Calif., performed the precipitation tests. She stated that the phenol present in the extracting fluid used in preparing the antigen will precipitate protein and thus tends to interfere with the proper performance of precipitin tests. Nevertheless, the tests were set up on the serums obtained before administration of the antigen and on those collected subsequently in the same manner. We believe the stronger reactions noted in the second series of tests are significant and tend to demonstrate that circulating antibodies can be produced in human subjects with injection of an antigen made from human skin.

COMMENT

The original concept of Whitfield supported by more recent clinical experience and modern experimental studies of sensitization has given us not only a definite clinical syndrome but also a valuable everyday approach to the better understanding of the eczematous processes.

The importance of the theory of autosensitization was emphasized by Ingram[11]: "That, in my view, is the aetiology of eczema in every case—a background of sensitiveness, an external provocation, and a degree of autosensitization once the eruption is in being."

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11. Ingram, J. T.: Definition and Aetiology of Eczema, Brit. J. Dermat. **47**: 502 (Dec.) 1935.

PSORIASIS AND ADRENOCORTICAL FUNCTION

A Preliminary Report on a Possible Steroid Hormonal Etiologic Relationship

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DESPITE numerous investigations, psoriasis still remains not only an etiologic puzzle but a therapeutic problem. The many failures to correct associated metabolic disturbances, revealed by biochemical observations, is a clear indication that the disease is not caused primarily by hemic changes, but is rather a result of hitherto unrecognized factors. Its frequent occurrence in Central and South China also eliminates the so often mentioned dietetic, racial and climatic preferences of the disease.

Among the many hypotheses which have been proposed to clarify the causation of psoriasis, hypofunction of the adrenal glands has been favored by many investigators (Grüneberg,[1] Riehl[2] and Kissmeyer, Chrom and Jacobson[3]). This assumption is based not only on the favorable response to adrenal cortical therapy but also on the observation that psoriasis is accompanied with a vitamin C depletion (Reiss[4] and Mage[5]) and responds favorably to its administration. Hypercholesteremia, generally associated with psoriasis, is considered due not only to hypothyroidism and altered hepatic function but to diminished activity of the adrenal cortex. It is of added significance that Bloch and Rittenberg[6] demonstrated that by using cholesterol tagged

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5. Mage, D.: La vitaminotherapie dans un cas de psoriasis rebelle et ancien, J. de méd. de Paris **28-29**:532, 1939.

6. Bloch, K., and Rittenberg, D.: The Biological Formation of Cholesterol from Acetic Acid, J. Biol. Chem. **143**:297, 1942.

with deuterium, not only the bile acids but also progesterone are formed from this steroid. Since progesterone is closely related structurally to the corticosterones, it is probable that the latter are formed from cholesterol. Furthermore, Zwemer, Lowenstein and Pines [7] isolated from the adrenal glands a water-soluble and biologically active steroid in which the steroid nucleus is linked with ascorbic acid. This may constitute further evidence that both ascorbic acid and cholesterol are necessary in the elaboration of some of the corticosteroids. Incendayi and Ottenstein,[8] based on their investigation of the cause of psoriasis, also assumed possible adrenocortical hypofunction. They found an elevation of blood serum potassium and observed a regression of lesions in 3 of their cases of psoriasis with a diet poor in potassium and adrenal-cortex medication, to which vitamins B_1 and B_2 were added. While LeWinn and Urbach [9] were unable to observe any beneficial effect after administration of adrenal cortical extract, it is of interest to note that Capelli [10] cleared up psoriasis and psoriatic erythroderma by the administration of sodium chloride. The relationship between the endocrine system and psoriasis was clearly demonstrated by the therapeutic results recently obtained with diethylstilbestrol by Frank.[11]

PRESENT INVESTIGATION

Twenty-five cases of psoriasis were investigated as to a possible adrenocortical disturbance. In addition to serum potassium, sodium and cholesterol, the glucose tolerance curve was determined as well as 17-ketosteroid excretion, vitamin C urinary excretion after the intravenous administration of 1 Gm. of ascorbic acid (saturation test) and sedimentation rate. Potassium was determined by the flame photometer and the 17-ketosteroids by the Zimmerman test. In a few instances the serum potassium tests were repeated after one week. The results are recorded in the table.

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7. Zwemer, R. L.; Lowenstein, B. E., and Pines, K. L.: Experimental Study of Similarities Between Cortin and Some Cardiac Glucosides, Endocrinology **27**: 945, 1940.

8. Incendayi, C. K., and Ottenstein, B.: Zur Frage der Behandlung der Psoriasis mit Kaliumarmer Diet und Nebennierenrindenextrakt, Dermatologica **80**:65, 1929.

9. LeWinn, E. B., and Urbach, E.: Low Potassium Diet in Treatment of Psoriasis, Arch. Dermat. & Syph. **51**:398 (June) 1945.

10. Capelli, E.: Versuche die Schuppenflechte mit chlorreicher Diet zu behandeln und die neueste Anschauungen über die Pathogenese, Atti Soc. ital. di dermat. e sif. **3**:730, 1940.

11. Frank, C.: Diethylstilbestrol as an Aid in the Treatment of Psoriasis, New York State J. Med. **47**:1790, 1947.

Results of Tests in Twenty-Five Cases *

Case No.	Age	Sex	Cholesterol	Sodium	Potassium	Result of Vitamin C Saturation Reaction Test	Result of Glucose Tolerance Test	Sedimentation Rate	17-ketosteroids	Blood Pressure, Systolic/Diastolic	Comment
1	14	M	200	294	27.0	242	90 111 80 85	2	2.2	100/ 60	
2	54	M	203	313	37.5 27.5	146	84 127 88 77	1	4.5	120/ 85	
3	71	M	255	313	22.5	176.6	106 249 211	34	5.1	110/ 80	Diabetic
4	54	M	224	373	27.5 28.6	94.5	121	7	7.8	120/ 80	
5	74	M	365	325	18.7	7.4	93 125 88 68	25	4.4	130/ 80	
6	54	F	325	325	19.4	140	94 100 71 60	17	6.8	150/100	
7	67	F	355	313	36.9 28.0	168	100 216 225 132	20	0.9	120/100	Diabetic
8	51	F	215	314	16.2	98	103 254 141 84	21	4.95	120/ 75	
9	56	F	230	319	18.8	156.6	104 132 124 107	39	1.24	110/ 80	
10	53	F	291	314	19.3	292	190 340 300 270	36	5.5	100/ 75	Diabetic
11	38	F	250	301	23.7	154	...	36	5.75	110/ 78	
12	31	F	220	314	13.8	116	101 88 90 62	..	5.7	105/ 75	
13	66	M	208	318 313	16.9 21.2	412	78 110 74 72	22	...	140/100	
14	49	F	252	301	20	232	65 108 58 36	25	2.2	110/ 70	
15	41	F	237	319	17.5	524	70	25	1.2	112/ 70	
16	34	F	211	293	....	...	...	33	...	100/ 70	
17	43	F	271	313	15.6	45	...	33	...	.....	

Results of Tests in Twenty-Five Cases—Continued*

Case No.	Age	Sex	Cholesterol	Sodium	Potassium	Result of Vitamin C Saturation Reaction Test	Result of Glucose Tolerance Test	Sedimentation Rate	17-ketosteroids	Blood Pressure, Systolic/Diastolic	Comment
18	58	M	242	350	18.75	225	...	16	...	.....	
19	48	M	190	338	18.1	36	184 342 196 108	21	7.35	105/ 70	Diabetic
20	38	M	650	325	20.0	152	80 106 84 69	4	2.4	110/ 70	
21	37	M	175	320	16.3	90	82 94 66 52	31	...	105/ 75	
22	43	F	184	306	16.25	87	...	37	4.3	110/ 80	
23	39	M	250	320	18.4	130	80 100 110 70	22	3.2	100/ 70	Arthropatic psoriasis
24	27	M	270	305	20	190	76 90 98 70	25	5.6	110/ 75	Arthropatic psoriasis
25	24	M	310	302	21	175	94 102 90	21	2.1	110/ 75	Arthropatic psoriasis

* The 17-ketosteroid determination was made by Dr. K. Dobriner at the Sloan-Kettering Institute and by Dr. E. J. Baumann, Montefiore Hospital.

RESULTS

The serum cholesterol level showed a definite variation ranging from 175 to 650, with an average of 263 mg. per hundred cubic centimeters. The serum sodium level was low in 2 cases (1 and 16) and low normal in 3 cases (11, 14 and 25); the rest showed normal levels. The serum potassium level was elevated in 4 cases, varying between 21.2 and 37.2 mg. per hundred cubic centimeters. In 5 patients (3, 6, 11, 14 and 20) there was a high normal level. In 2, reexamination gave much higher values than did the previous determination (4 and 13). The vitamin C saturation test showed, except in 1 case, a definite depletion, with the extreme low level of 7.4 mg. in 1 instance. The glucose tolerance test showed in a few instances a rather flat curve. The urinary excretion of 17-ketosteroids was significantly low, varying between 1.24 and 7.80. Despite the high age group of some of the patients, the figures were below normal. Similarly significant was the increased sedimentation rate in 11 cases, with a maximum of 39 in case 9. It was of interest that blood pressures were rather low despite the advanced age of most of the patients.

COMMENT

Though the skin of psoriatic patients contains higher amounts of water (77 per cent) than normal (62 to 64 per cent), it is questionable

whether this alteration could be interpreted as a functional weakness of the electrolyte-regulating hormones of the adrenal cortex. In addition, there is increased capillary permeability, not necessarily due solely to a disturbance of electrolyte balance but possibly to diminished function of the medulla. The decreased secretory activity of the cortex in rats with demedullated adrenal glands was demonstrated by Swann and Fitzgerald,[12] Eversole, Edelmann and Gaunt[13] and Wyman and tum Suden.[14] On the basis of these experiments, it can be assumed that combined hypofunction of the cortex and medulla may be present. This would also explain the cutaneous vascular dilatation and the edema of the dermis and epidermis. It is probable that such may be the case in psoriasis, since no uniform or significant disturbance in the electrolytic balance was demonstrable in any patient studied. This is supported by the fact that, despite the increase of potassium in 5 patients, a moderate decrease of sodium was observed. The increase of cholesterol in psoriasis may be of greater significance than hitherto considered. The fact that cholesterol, one of the building stones of cortical steroids, may be present in increased amounts not only in the serum but also in the adrenals could be interpreted as a disturbed corticohormonal function. This is borne out by Sayers and his co-workers,[15] who found that single injections of this trophic hormone decreased the cholesterol content of the adrenal by some 50 per cent in three to six hours and the return to normal levels took several hours. The fact that Incendayi[8] produced an obvious and immediate aggravation of the lesions after the oral administration of 10 Gm. of cholesterol in 100 cc. of olive oil (cholesterol saturation test) may be a further indication of an upset biosynthesis or disturbance in the secretion of cortical hormones.

In most of the cases here reported an appreciable vitamin C depletion was present. It is conceivable that vitamin C depletion may be related to deficiency of the adrenal cortex, which normally contains high amounts of vitamin C and which is essential for its normal function. Supporting this view is Long's experience. He stated that as a result of his experience he felt that more significance could be attached to

12. Swann, H. G., and Fitzgerald, J. W.: Insulin Shock in Relation to the Components of the Adrenals and the Hypophysis, Endocrinology **22**:687, 1938.

13. Eversole, W. J.; Edelmann, A., and Gaunt, R.: Effect of Adrenal Cortical Transplants on Life Maintenance and Water Intoxication, Anat. Rec. **76**:271, 1940.

14. Wyman, L. C., and tum Suden, C.: Redistribution of Body Fluids After Glucose Injections in Rats with Adrenocortical Transplants, Endocrinology **31**: 295, 1942.

15. Sayers, G.; Sayers, M. A.; Lewis, H. L., and Long, C. M. H.: The Effect of Adrenotrophic Hormone on Ascorbic Acid and Cholesterol of the Adrenal, Proc. Soc. Exper. Biol. & Med. **55**:238, 1944. Sayers, G.; Sayers, M. A.; Fry, E. G.; White, A., and Long, C. H: The Effect of the Adrenotrophic of the Anterior Pituitary on Cholesterol Content of the Adrenals, Yale J. Biol. & Med. **16**:361, 1944.

ascorbic acid determination since "these findings reflect more rapidly than the cholesterol content on the secretory activity of the cortex of the adrenal."

A possible further indication of disturbed corticosteroid hormonal function is the diminished excretion of 17-ketosteroids. Since it is an established fact that female and male castrates excrete significant amounts of 17-ketosteroids, it could well be assumed that the diminished excretion of 17-ketosteroids in psoriasis might be due largely to a diminished adrenal cortical function.

The well known observation that the lesions of psoriasis subside or disappear entirely in most parturient women toward the end of pregnancy, when steroid hormones reach a high peak, is a link in the pathogenesis of psoriasis. Most patients relapse soon after delivery. There may be a causal relationship with pituitary hyperfunction, which in turn stimulates the cortex of the adrenals, thyroid and gonads as well. This is a clear indication that, with the cessation of overproduction of estrogenic hormones, progesterone and corticoadrenal hormones, keratin formation in the affected areas is also disturbed. The clinical observation that psoriasis also subsides during attacks of jaundice might also be of some interest in this connection. The close structural relationship between desoxycholic acid and corticosterones has been known for a long time. Long reported recently that the partial synthesis both of dehydrocorticosterone and 11-dehydro-17-hydroxycorticosterone from desoxycholic acid has been accomplished, which may explain the fact that jaundiced patients with psoriasis show improvement. It appears, therefore, that some relationship exists between the two diseases and that further investigation might throw light on a possible solution of the pathogenesis of psoriasis.

This disturbance in keratin formation in psoriasis may well be associated with a disturbed corticoadrenal function. Adrenal cortical tumors with increased hormonal production are accompanied with hirsutism. As the chemical content of hair and epidermal keratin is similar, the possibility exists that hirsutism, on the one hand, and parakeratosis, on the other, are expressions of hyperfunction and hypofunction of certain adrenal steroid hormones respectively.

The possibility of an infectious agent as the cause of psoriasis has been suggested many times. There have been numerous observations that it has its onset with acute tonsillitis or pharyngitis and, furthermore, that the removal of foci of infection, of teeth, tonsils, gallbladder and the like, effects a prompt cure. In addition to these valuable clinical observations, it should be mentioned that during the recent mass vaccinations against variola, 5 patients with postvaccinal psoriasis were observed by me, in all of whom psoriasis developed around the eighth

to ninth day after vaccination; similarly, 4 cases of erythema multiforme appeared about the same time after vaccination. It is contestable whether the vaccine virus sensitized the skin and produced the well known parakeratotic changes clinically expressed in the form of psoriasis or whether a kind of biotropism should be considered which provoked a latent infection. That in such instances the adrenal cortex could be involved is also a plausible hypothesis, since it is well known that damaging agents, such as certain toxins (diphtheria), burns, severe pellagra and pemphigus, may seriously interfere with adrenal function. The well known aggravation of psoriasis after mental stress may also be explained in the light of recent experiments by Long, who observed that epinephrine may cause an increased utilization of cortical hormones by the tissues or change the composition of blood passing through the anterior lobe of the pituitary gland. There also appears to be a lack of adrenal-like substances in psoriatic patients. This is borne out by the fact that not only is there diminished pigmentation in the lesions, but the entire skin lacks pigment formation. This statement would not exclude an accompanying adrenocortical deficiency, because there are some authentic cases of Addison's disease on record in which there was no hyperpigmentation of the skin or mucous membranes. Furthermore, the relationship between the pigmentation of the skin seems more closely related to substances which are chemically allied to epinephrine. In this connection I can also confirm the results of experiments of Ehrmann [16]: the serum of psoriatic patients lacks epinephrine-like substances and does not cause a dilatation of the pupils of the isolated frog eyes, as demonstrated with the serums of 4 patients, in contrast to results with control serums (unpublished data).

CONCLUSION AND SUMMARY

The number of cases investigated is not sufficient to permit definite conclusions. There appears to be an indication that the pathogenesis of psoriasis seems to be associated with disturbed steroid hormonal production, the seat of which may be in the cortex of adrenals, but a pituitary relationship cannot be denied. This assumption is based on the following observations:

1. Diminished 17-ketosteroid excretion was present in 12 cases, 2 eliciting normal low values.

2. A flat glucose tolerance curve was present in 9 cases (cases 2, 5, 6, 12, 20, 21, 23, 23 and 25).

3. A vitamin C depletion was present in 22 patients.

16. Ehrmann, R.: Eine physiologische Wertbestimmung des Adrenalins und seinen Nachweis im Blut, Arch. f. exper. Path. u. Pharmakol **53**:96, 1905.

4. In 5 cases an increase of serum potassium is noted, with a decrease of sodium in 3.

5. In 5 cases an appreciable increase of cholesterol was recorded, with high normal values in the rest.

6. The blood pressure was low, particularly in persons of the older age group (cases 3, 10, 13 and 15).

The increased sedimentation rate indicates an infectious or toxic cause, which seems to be highly possible, based not only on the observation that removal of septic foci is curative in certain cases but also on the recent observation that psoriasis developed in 5 cases after vaccination against smallpox.

NEUROSYPHILIS

Penicillin and Malarial Fever Therapy Versus Penicillin and Vaccine (Typhoid) Fever Therapy

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THIS REPORT includes data relating to 15 patients treated with vaccine (typhoid) fever and penicillin and 17 patients treated with malarial fever and penicillin. About 80 per cent of the patients in each group had dementia paralytica or the tabetic form of dementia paralytica, the remaining 20 per cent having asymptomatic neurosyphilis, tabes dorsalis or meningovascular neurosyphilis.

The technic used in administering vaccine fever is similar to the continuous intravenous infusion method as used by Heyman.[1]

TECHNIC OF VACCINE FEVER THERAPY

1. The temperature is held above 103 F. (axillary) from five to ten hours, depending on the condition of the patient.

2. The temperature is usually maintained around 104.5 F. (axillary) if possible, as this is the optimum temperature.

3. The temperature, pulse rate and rate of respirations are recorded at fifteen minute intervals while the temperature is above 102 F. (axillary) or whenever there is any doubt as to the temperature.

4. All temperatures are taken by placing the thermometer in the axilla.

5. The pulse rate is taken at the temporal or carotid arteries.

6. Danger signals of exhaustion of the patient are present when the pulse rate equals or exceeds 160, the respirations equal or exceed 60 or the temperature equals or exceeds 105.5 F. (axillary).

7. No water is given to the patient unless the temperature rises above 105 F. (axillary).

8. Temperature which is dangerously high, i.e., above 105.5 F. (axillary), may be reduced by freeing one or two arms, giving the patient a sip of water, removing some blankets or giving an alcohol sponge bath, if needed.

9. The patient is restrained and covered with one to six blankets from the beginning of the administration of the typhoid vaccine until he has received all of his fever therapy for the day.

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1. Heyman, A.: The Treatment of Neurosyphilis by Continuous Infusion of Typhoid Vaccine, Ven. Dis. Inform. **26**:51-57 (March) 1945.

10. Vaccine fever therapy is given three times weekly. Breakfast is omitted on these mornings.

11. The first dose of typhoid vaccine is 25,000,000 organisms given intravenously with a syringe. If this dose is not capable of causing an elevated temperature, the dose is doubled each succeeding day until fever results. Subsequently the dose is increased about 60 per cent each time. The typhoid vaccine is placed in two bottles of 1,000 cc. of 5 per cent dextrose in 0.9 per cent isotonic sodium chloride solution and administered intravenously.

12. When only 50 to 100 cc. remain in the first bottle, it is removed and the second bottle is connected to the same tubing. This procedure obviates the necessity of using two sets of tubing and, also, the reinsertion of a second needle.

13. Sodium "amytal" (sodium isoamylethylbarbiturate), 3¾ grains (244 mg.) may be given into the tubing of the second bottle. It may be repeated intramuscularly whenever sedation is indicated.

14. Morphine sulfate, ¼ grain (16.25 mg.), may be used intramuscularly every four hours during the severe fever only as indicated.

15. Administration from the second bottle is discontinued only when the temperature goes above 102 F. (axillary); otherwise, all of the solution is allowed to go into the vein.

16. When the temperature finally falls below 102 F. (axillary) in the downward curve after the major portion of the fever has been completed, the blankets are removed and the fever therapy discontinued. The blankets are also removed when the patient has had from five to ten hours of temperature over 103 F. (axillary), depending on the condition of the patient.

17. A high protein, high caloric diet is given, with vitamin C, 200 mg., and 2 vitamin B complex capsules daily if possible.

Crystalline penicillin sodium G was given to both groups of patients receiving fever therapy. The dose was 100,000 units every three hours, given intramuscularly for twenty-five days, making a total of 20,000,000 units. In 2 patients receiving vaccine fever therapy, sensitivity to penicillin developed, but both of them had received over 10,000,000 units before treatment with the drug was discontinued.

Effective fever as used in both groups of fever therapy, was arbitrarily defined as the number of hours the patient's temperature remained at 103 F. (axillary) or over.

The average age of the group receiving typhoid vaccine was 41 years; that of the group receiving therapeutic malaria was 44 years. One fourth of the patients receiving typhoid vaccine were 50 years of age or over, while one-half the patients receiving malarial fever therapy were 50 years or over. However, there were fewer complications with the group receiving malarial fever therapy, in spite of the fact that it was an older group.

COMPLICATIONS OF VACCINE FEVER THERAPY

Herpes simplex occurred in 87 per cent of the patients, usually during the first portion of the course of vaccine fever therapy. It usually followed a benign course, but occasionally it was extensive,

involving the lips, chin and cheeks. In 1 case it involved the cornea of the eye. With conservaive medication it healed in three weeks, with no impairment of vision.

Trophic ulcers occurred in 1 out of 3 patients. The involved areas were usually on one or both heels. In 1 case it was located over the sacrum and in another case over the head of the fibula. All these ulcers were caused by the weight of the blankets and the long period the patient remained in one position. The ulcers on the heels could have been prevented to some extent by elevating the blankets at the foot of the bed and by placing a folded blanket beneath the legs in order to elevate the heels. Of course, the patient could not shift his position in bed if the restraining sheets were effective in keeping him beneath the blankets and in maintaining effective fever.

A relapse with paretic manifestations occurred in 3 cases in the vaccine therapy group. The patients began having auditory hallucinations, delusions of grandeur and less contact with their environment. A relapse with tabetic manifestations occurred in 2 cases. One patient entered the hospital with the single observation of optic atrophy. After forty-two and a half hours of effective fever, partial paralysis and tingling and numbness of the lower extremities and hands suddenly developed. Severe vomiting and malaise were also present.

Severe shock and uremia occurred in 2 patients. This occurred with the first chill after each patient received over 700,000,000 organisms. Severe uremia ensued in three days, at which time the nonprotein nitrogen of the blood was observed to be 170 and the creatinine 5.4. One of these patients also had deep jaundice, while the other had paradoxic incontinence, requiring a retention catheter for two weeks. Both patients appeared completely recovered from these episodes after four weeks.

Another patient had a severe reaction (pulse rate of 170, temperature of 106.6 F. [axillary], delirium and shock) after only 100,000,000 organisms as an initial dose. However, he completed his typhoid course uneventfully without any delay or ill effects.

Singultus, lasting for one week, occurred in 1 case. Mild transient anemia occurred in only 1 case. Another patient experienced a temperature of 108.2 F. (axillary) without ill effects.

Another serious complication from the vaccine fever therapy was a patient's inability to withstand the unpleasant medication. Six of the patients who had received vaccine fever therapy at first and later received malarial fever therapy preferred the malaria without reservation. The 2 patients who refused the vaccine fever therapy were serious when they said they would rather die of syphilis than receive

more typhoid vaccine. Opiates and barbiturates helped to relieve the discomfort, but frequent doses fell far short of relieving an inherently severe form of fever therapy.

REASONS FOR PREMATURE CESSATION OF VACCINE FEVER THERAPY

The reasons for premature cessation of vaccine fever therapy were: fear of treatment by the patient (2 cases), shock and uremia (2 cases), high typhoid vaccine dosage (2 cases) and relapse with tabetic manifestations (1 case).

More patients might have discontinued the vaccine fever therapy because of fear of the severe discomfort associated with it. However, much persuasion was successful in convincing the patients to continue with the typhoid vaccine.

After a dose of 90,000,000,000 typhoid organisms per chill was reached, the fever was stopped because of fear of the effect of such high dosages.

After a severe relapse with tabetic manifestations in a patient receiving vaccine fever therapy, it was felt that this patient would better withstand malarial fever therapy in completing his course of fever therapy. The course of therapeutic malaria was subsequently completed without difficulty.

COMPLICATIONS OF MALARIAL FEVER THERAPY

The complications of malarial fever therapy were few and not of serious nature. There were no cases of jaundice, edema, renal damage, peripheral neuropathy, shock, relapse with tabetic or paretic manifestation or trophic ulcers.

Severe weakness, occurring toward the end of the course of therapeutic malaria was seen in 30 per cent of the patients. If the patient had not had a sufficient number of effective hours of malarial fever therapy by this time, "thio-bismol" (sodium bismuth thioglycollate), 0.2 Gm., was given intramuscularly, as recommended by Cole and his co-workers.[2] This drug was effective in causing a remission of the malarial fever for two to seven days. During this rest interval the patient gained much strength, enabling him to continue his fever therapy for a longer time. After cessation of the malarial fever therapy, the weakness disappeared within one to three weeks.

Anemia, appearing in 30 per cent of patients receiving therapeutic malaria, was always of a mild grade, the blood cell count never going

2. Cole, H. N.; De Oreo, G. A.; Driver, J. R.; Johnson, H. H., and Schwartz, W. F.: Use of Bismuth Injections to Manage Course of Therapeutic Malaria, J. A. M. A. **115**:422-427 (Aug. 10) 1940.

below 2,800,000 erytherocytes or 6 Gm. of hemoglobin. The erythrocyte count and hemoglobin correlated well with the strength of the patient in malarial fever therapy, both decreasing and increasing together.

Herpes simplex occurred about one fourth as frequently in malarial fever therapy as in vaccine fever therapy. Also, its severity was usually less in therapeutic malaria.

Vomiting occurred in about 20 per cent of the cases. Sodium bismuth thioglycollate afforded temporary relief of the vomiting. Severe vomiting prevented completion of an adequate course of malarial fever therapy in only 1 of the 17 cases.

One patient had a urinary infection, proved by culture to be from Proteus vulgaris. It occurred at the termination of the malarial fever therapy. Sulfathiazole caused the temperature to return to normal in two days. This patient had had urinary retention during a previous course of vaccine fever therapy.

LABORATORY STUDIES

An attempt was made to discover some laboratory method of determining the relative stamina of a patient during the course of fever therapy. If some test could be performed at regular intervals which would indicate when the patient's ability to withstand the treatment was decreasing to a dangerous point, complications and death might be more certainly avoided.

The serum proteins and albumin-globulin ratio were followed carefully throughout the course of both malarial and vaccine fever therapy. However, this information did not materially contribute toward a more accurate clinical evaluation of the patient's status.

During vaccine fever therapy there was no case in which the serum proteins were less than 5.0 Gm. per hundred cubic centimeters. Also the albumin-globulin ratio was not reversed, except in 1 case four months after treatment.

At the end of the course of therapeutic malaria, the serum protein and albumin-globulin ratio dropped to 4.8 Gm. per hundred cubic centimeters and 3.3 : 1.5 in 1 case, and 4.5 Gm. per hundred cubic centimeters and 3.3 : 1.2 in another. However, in another case, the reading was 4.8 Gm. per hundred cubic centimeters and 4.0 : 0.8 in the middle of the fever course. This patient continued his fever for a total of sixty-seven and a half hours of effective fever and twenty-three paroxysms of fever, after which the reading was 7.5 Gm. per hundred cubic centimeters and 3.6 : 3.9. Feldman and Murphy [3] ex-

3. Feldman, H. A., and Murphy, F. D.: Effect of Alterations in Blood Volume on Anemia and Hypoprotenemia of Human Malaria, J. Clin. Investigation **24**:780-792 (Nov.) 1945.

pressed the opinion that the hypoproteinemia in malaria in human beings was due to hemodilution.

The average reading of serum proteins and albumin-globulin ratios in vaccine fever therapy was 6.9 Gm. per hundred cubic centimeters and 4.5 : 2.3, while that of malarial fever therapy was 6.2 Gm. per hundred cubic centimeters and 3.8 : 2.4. These averages show a tendency for the total serum protein and the serum albumin to be lower during therapeutic malaria. The albumin-globulin ratio was less than 1.0 in 12 per cent of patients receiving malarial fever therapy, whereas it did not occur during vaccine fever therapy in any of the patients. However, no patients showed any clinical edema as a result of this adverse serum protein ratio.

Erythrocyte counts and hemoglobin determinations were done throughout both malarial and vaccine fever therapy. The tests were good indexes of stamina in therapeutic malaria but not in vaccine fever therapy. In the patients receiving malarial fever therapy the erythrocyte count fell below 3,600,000 and hemoglobin below 70 per cent at the end of treatment in 3 out of 10 cases. Studies in blood changes after inoculation with malaria [4] indicate that soon after the inoculation there is evidence of a stimulation effect on red blood cell formation, which is followed by the typical malarial anemia.

CLINICAL RESULTS

Of the 9 patients who received an adequate course of vaccine fever therapy and penicillin, 3 were improved, 2 showed no improvement and 4 were worse. Similarly, of the 13 patients completing a full course of malarial fever therapy and penicillin, 10 were improved, 2 were unchanged and 1 was worse. Thus, 77 per cent of the patients receiving therapeutic malaria showed clinical improvement, while only 33 per cent of the patients receiving vaccine fever therapy showed improvement. It is also important to note that 44 per cent of the patients receiving vaccine fever therapy were clinically worse while only 8 per cent of the patients receiving malarial fever therapy were worse.

The 6 patients receiving vaccine fever therapy who showed no improvement or became worse simultaneously received crystalline penicillin sodium G, 100,000 units given every three hours intramuscularly, for a total of 20,000,000 units in 4 cases and 14,400,000 and 10,000,000 units in the other 2 cases. These results suggest that penicillin does not improve the course of paresis to any appreciable extent.

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4. Pijper, A., and Russell, B. D.: Incubational Changes in the Red Cell Count in Innoculated Malaria, Brit. M. J. **2**:620-621 (Oct. 4) 1914.

Callaway and his co-workers,[5] who treated all types of neurosyphilis, used penicillin alone, 50,000 units every three hours for eighty doses, or 4,000,000 units. Ninety-one per cent of his patients showed clinical improvement and 64 per cent showed improvement in the spinal fluid observations.

O'Leary and his co-workers[6] reported that penicillin in combination with fever therapy, either malarial or by means of the fever machine, did not improve the clinical results noted from fever treatment alone. They stated the belief that treatment with penicillin alone is not capable of controlling the parenchymatous forms of neurosyphilis. Results in this series of cases are in accord with these beliefs, in spite of the much higher dosages of penicillin used here.

This report is at complete variance with that of Lascara,[7] who stated that 84 per cent of the patients treated with artificial fever were improved, whereas only 48 per cent of the patients receiving therapeutic malaria were benefited. He stated the belief that artificial fever was also better than malaria in that it was tolerated more readily and had fewer treatment complications.

COMMENT

It is possible to produce in a patient as many hours of effective fever with malaria fever therapy as with vaccine fever therapy. In this series of cases the patients receiving therapeutic malaria had few mild complications as compared with those receiving vaccine fever therapy.

The technic involved in administering vaccine fever therapy was more difficult and more hazardous and required much more work by the attendants, nurses and doctors than did therapeutic malaria. The patients preferred malarial rather than vaccine fever therapy because of the comparative ease and comfort with which they endured effective fever with therapeutic malaria. In an uncooperative patient malarial fever therapy was easily possible, whereas vaccine fever therapy was extremely difficult in an actively psychotic patient.

An argument often used against malarial fever therapy is that there were then two diseases to treat instead of only one. All these patients with syringe-inoculated tertian malaria were promptly cured, and no relapse of the malaria was experienced, after receiving a total of 3.2 Gm. of quinacrine hydrochloride in six days. If the patient was vomiting and

5. Callaway, J. T.; Noojin, R. O.; Flower, A. H., Jr.; Kuhn, B. H., and Riley, K. A.: The Use of Penicillin in the Treatment of Syphilis of the Central Nervous System: Report of One Hundred Patients, Am. J. Syph., Gonor. & Ven. Dis. **30**:110-124 (March) 1946.

6. O'Leary, P. A.; Brunsting, L. A., and Ockuly, O.: Penicillin in the Treatment of Neurosyphilis, J. A. M. A. **130**:698-700 (March 16) 1946.

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unable to take the drug orally, it was given intramuscularly with equal success and facility. Engstrom and his co-workers [8] also reported no relapse in syringe-inoculated tertian malaria after treatment by a similar schedule.

Patients receiving malarial fever therapy rarely required opiates or barbiturates during fever. A patient receiving therapeutic malaria could have a temperature of 103 to 105 F. (axillary) with a surprising lack of discomfort. This phenomenon was especially evident when compared with the discomfort experienced by a patient with the same temperature who was receiving vaccine fever therapy.

Two simple laboratory procedures aided in estimating the resistance of a patient receiving malarial fever therapy, whereas none were helpful in judging the condition of a patient receiving vaccine fever therapy. Clinical appearance of the patient proved to be the most reliable method of judging the patient's ability to withstand further fever therapy. With the aid of sodium bismuth thioglycollate and quinacrine hydrochloride, the amount and frequency of malarial chills could be controlled as easily as could the frequency and amount of typhoid fever. Thompson [9] and Shield [10] reported the successful use of therapeutic malaria in the home. However, the difficulties attending the home use of vaccine fever therapy with the technic as used here would be insurmountable.

SUMMARY

From the point of view of comfort to the patient and ease of administration, malarial fever therapy was far superior to vaccine fever therapy. In malarial fever therapy the percentage of patients who were improved was much greater, and the percentage who were worse was much less, than in vaccine fever therapy. There were fewer and less serious complications with therapeutic malaria than with vaccine fever therapy. There were no malarial relapses after the patient was treated with 3.2 Gm. of quinacrine hydrochloride over a six day period.

In malarial fever therapy the laboratory tests found to be useful in judging the condition of the patient were the erythrocyte count and hemoglobin determination. A laboratory test which would aid in evaluating the condition of a patient receiving vaccine fever therapy was not found. Crystalline penicillin sodium G, 20,000,000 units given over a period of twenty-five days, seemed to be of minimal or no benefit in cases of paresis and the tabetic form of dementia paralytica. There were no deaths with either form of fever therapy.

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INFLUENCE OF TETRA-CHLORO-PARA-BENZOQUINONE ON HUMAN FUNGOUS INFECTIONS

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IN PRELIMINARY clinical trial, tetra-chloro-para-benzoquinone in high concentration proved nontoxic when applied to the human skin as an ointment.[1] Moreover, it was therapeutically active in the treatment of various forms of tinea capitis.[1] For a number of years an impure preparation of this drug, spergon® (a mixture of chemically pure tetrachloroparabenzoquinone, 99 per cent, and disodium phosphate, 1 per cent, manufactured by the United States Rubber Company), has been successfully used as a protectant for the control of fungi that attack seeds.[2] The present report deals with further experiences in the management of tinea capitis as well as several other human fungous infections.

MATERIALS AND METHODS

Cases were obtained from the dermatologic clinic of a general city hospital and from private practice. Fifty-one of the total of 155 patients were hospitalized, not because of the greater severity of their lesions, but in order to control them more closely and to carry out initial testings of increasing concentrations of the drug. No one of the 135 children with tinea capitis was more than 11 years old; the average age was 6.1 years. One hundred and one of these were boys and 34 girls.

As in the preceding study,[1] details of the individual case, such as the size and number of lesions, the duration of the condition and other historical data, were apparently irrelevant to an evaluation of

1. Collins, J. G.; McGavack, T. H., and Boyd, L. J.: The Effect of Tetra-Chloro-Para-Benzoquinone upon Human Fungus Infections: I. In Vitro and in Vivo Studies with Tinea Capitis, Urol. & Cutan. Rev. **50**:276, 1946.

2. McGavack, T. H.; Boyd, L. J.; Terranova, R., and Lehr, D.: Toxicity Studies with the Fungicide Tetra-Chloro-Para-Benzoquinone (Spergon), J. Indust. Hyg. & Toxicol. **25**:98, 1943.

the action of the drug. The same statement applies to the corresponding facts obtained in cases with fungous lesions other than tinea capitis. Therefore, all such data have been omitted from the present report. Suffice it to say that the number, size and appearance of the lesions and their duration failed to show any close relationship to the course of the condition as affected by treatment. All methods, including the identification of organisms, other diagnostic procedures and the manner of caring for the scalp and applying ointments, are as previously described.[1]

The drug was applied as an ointment, representing concentrations varying from 5 to 50 per cent, and as a powder, undiluted and diluted with equal parts of powdered talc.[3] Three ointment bases were employed: (1) equal parts of wool fat and white petrolatum, (2) an oil-in-water emulsion of anhydrous wool fats[4] and (3) a wetting agent base, consisting of 2 per cent sodium lauryl sulfate in equal parts of cholesterol, anhydrous wool fat and white petrolatum.[5]

RESULTS

The results obtained by the application of tetra-chloro-para-benzoquinone to human fungous infections are summarized in tables 1, 2 and 3.

A. Tinea Capitis Due to Microsporon Audouini.—Inasmuch as this is one of the most difficult fungous infections to cure, the major portion of our effort was directed toward its control (table 1). Application of the drug as a powder was totally ineffective. Of the three ointment bases, omnia creme® proved unsatisfactory when the tetra-chloro-para-benzoquinone was combined with it in a concentration of 5 per cent. Under these conditions, the irritation of the scalp was so severe that treatment had to be discontinued at the end of several days in every instance. Moreover, during this period of time, the preparation did not materially influence the course of the infection. Because of the latter fact, lesser concentrations of spergon were not tried.

The wool fat and petrolatum and the oil-in-water (amerchol®) bases both proved to be satisfactory mediums for the effective application of spergon.® It is clear from table 1 that the percentage of cures with the amerchol® base is about twice that obtained with a

3. Generous supplies of spergon® powder were made available through the courtesy of Dr. T. W. Brasfield of the Naugatuck Division of the United States Rubber Company.

4. Obtained from the American Cholesterol Products Company, Milltown, N. J., under the trade name, amerchol.

5. Obtained from the Dome Chemical Company, Brooklyn, under the trade name, omnia creme.

corresponding concentration of the wool fat and petrolatum base. For instance, in a 20 per cent preparation, there were 27.8 per cent cures with the former base as compared with 14.3 per cent with the latter;

TABLE 1.—*The Effect of Tetra-Chloro-Para-Benzoquinone on Tinea Capitis Due to Microsporon Audouini*

Base	Drug Concentration, Percentage	Average Duration of Treatment, Weeks	Results (Number of Cases) Total	Cured	Improved	Unchanged	Relapsed	Percentage Cured
I. Wool fat-petrolatum *	5.0	4.0	10	2	5	3	2	20.0
	15.0	3.0	7	1	6	0	1	14.3
	20.0	5.8	7	1	6	0	0	14.3
	25.0	2.5	5	1	4	0	1	20.0
	50.0	2.0	7	3	4	0	0	42.9
Total	....	...	36	8	25	3	4	22.2
II. Amerchol ® †	7.5	2.0	7	1	4	2	1	14.3
	10.0	5.0	10	1	9	0	0	10.0
	20.0	6.7	11	3	8	0	0	27.8
	30.0	3.8	10	4	5	1	1	40.0
	50.0	2.0	10	7	3	0	0	70.0
Total	....	...	48	16	29	3	2	33.3
Total I and II	....	...	84	24	54	6	6	28.6
III. Omnia creme ® ‡	5.0	0.7	3	0	0	3	..	0.0
IV. Talc §	50.0	5.0	4	0	0	4	..	0.0
V. None ‖	100.0	2.0	5	0	0	5	..	0.0
Grand Total	....	...	96	24	54	18	6	25.0

* Equal parts of wool fat and white petrolatum.
† Amerchol ® is an oil-in-water emulsion of anhydrous wool fats.
‡ Omnia creme ® is a wetting agent base consisting of 2 per cent sodium lauryl sulfate in equal parts of cholesterol, anhydrous wool fat and white petrolatum.
§ The tetra-chloro-para-benzoquinone powder was diluted with an equal portion of powdered talc.
‖ Undiluted tetra-chloro-para-benzoquinone powder was applied.

TABLE 2.—*Effect of Tetra-Chloro-Para-Benzoquinone on Tinea Capitis not Due to Microsporan Audouini*

Base	Concentration of Spergon, ® Percentage	Average Duration of Treatment, Weeks	Results (Number of Cases) Total	Cured	Improved	Unchanged	Relapsed	Cured, Percentage
Wool fat-petrolatum *	5.0	5.4	9	3	6	0	0	33.3
Amerchol ® †	7.5	6.0	16	9	7	0	0	56.2
	10.0	3.5	13	11	2	0	0	84.6
	20.0	10.0	1	1	..	..	..	100.0
Total	....	...	39	24	15	0	0	61.6

* Equal parts of wool fat and white petrolatum.
† Amerchol ® is an oil-in-water emulsion of anhydrous wool fats.

similarly, at 50 per cent strength these figures rose to 70.0 and 42.9 per cent, respectively. The percentages of cures were 22.2 and 33.3 per cent for all cases in which the treatment used was tetra-chloro-parabenzoquinone in wool fat and petrolatum and in amerchol,® respectively. Of 84 patients treated with the drug in one or the other of these

mediums, 24 were completely cured, 54 improved, 6 were not helped and 6 were subject to relapse after apparent cure (table 1). Three of those who were cured by the application of the benzoquinone derivative, 30 per cent strength in an amerchol® base, had had recurrence following epilation with roentgen rays.

B. Tinea Capitis Due to Other Organisms Than Microsporon Audouini.—Of the 39 cases in this group, 35 were due to Microsporon felineum, and 4 to Microsporon lanosum. Here, again the amerchol® base proved to be more effective than the wool fat and petrolatum medium (table 2), so that most of the studies were carried out with tetra-chloro-para-benzoquinone in the former material. Twenty-four of the 39 patients were cured and 15 improved. There were no relapses. Effective concentrations of the drug were lower than those necessary to similarly influence infections due to M. audouini (tables 1 and 2). At concentrations of 10 per cent and above, reasonable persistence in treatment usually eventuated in cure.

The length of time treatment with tetra-chloro-para-benzoquinone should be continued seems to have been fairly well determined. If the infection shows no change in fluorescence within the first two weeks, further treatment seems futile. If, however, there is improvement, then the treatment should be continued. If the patient is not freed of infection by the fifth or sixth week, as shown by the Wood filter and cultures, then further treatment will probably not be helpful. These statements apply to all the infections studied.

C. Fungous Infections Other Than Tinea Capitis.—1. Tinea: No one of 5 cases of tinea cruris was materially helped by one week of treatment with a 5 per cent ointment of spergon® in a wool fat-petrolatum base. Indeed, 2 of the patients with weeping lesions were made worse. A mixture of equal parts of spergon® powder and powdered talc was also tried in these patients. In the cases in which there were weeping lesions there was a tendency to "caking" and "crusting," but no apparent influence could be observed on the underlying condition. In 1 case each of tinea favus and tinea versicolor there was no response to five and four weeks of treatment, respectively, with spergon® 5 per cent in a wool fat-petrolatum base.

2. Epidermatophytosis: In all, 15 patients with epidermatophytosis (table 3) were treated with spergon.® Four of these received daily or twice daily applications of 5 per cent spergon® in the wool fat-petrolatum base; 1 was improved. Treatment was discontinued in the other 3 at the end of one week, as the lesions were worse. However, in all 3 of these, tetra-chloro-para-benzoquinone (100 per cent) as a powder in the shoe and on the lesions effected a cure. Seven

of 11 additional patients, who used the powder, were completely cured. The failures occurred in persons whose feet perspired freely. Irritation from the drug was always more noticeable the greater the amount of moisture present.

COMMENT

The fungicidal activity of tetra-chloro-para-benzoquinone depends, at least in great part, on the loosely combined chlorine atoms, which are relatively stable in acid mediums, but soluble and active in the presence of alkalinity. Its ability to influence fungous infections in

TABLE 3.—*Effect of Tetra-Chloro-Para-Benzoquinone on Miscellaneous Human Fungous Infections*

Condition	Drug: Preparation	Drug: Percentage	Average Duration of Treatment, Weeks	Results (Number of Cases): Total	Cured	Improved	Unchanged	Relapse	Cured, Percentage	Comment
Tinea										
(*a*) Cruris	Wool fat-petrolatum *	5.0	1.0	3	0	0	3	..	0.0	Aggravation in all 3
(*b*) Favus	Wool fat-petrolatum *	5.0	5.0	1	0	0	1	...	0.0	
(*c*) Versicolor	Wool fat-petrolatum *	5.0	4.0	1	0	1	0	..	0.0	
Epidermatophytosis	Wool fat-petrolatum *	5.0	1.0	4	0	1	3	0	0.0	In ambulatory patients condition was aggravated
	Powder †	100.0	2.5	11	7	3	1	0	63.3	
Total		....	...	20	7	5	8	0	35.0	

* Equal parts of wool fat and white petrolatum.
† Undiluted tetra-chloro-para-benzoquinone powder was applied.

the human being is due not only to this fact but also to its reasonably effective penetration of the upper layers of the skin and its emunctories.

The amount and concentration of the drug which can be safely used vary somewhat with the condition of the skin and the base employed. In general, the more irritated or excoriated the skin, the less the amount of drug tolerated. Wetting agents, such as sodium lauryl sulfate, increase the penetrability of the skin and produce a degree of irritation commensurate with the penetration attained.

Tetra-chloro-para-benzoquinone is freely miscible with oily bases; equal parts of wool fat and white petrolatum make a reasonably satisfactory medium. However, oil-in-water emulsions of the cholesterol-wool fat type, such as amerchol,® have proved more satisfactory in our hands. They do not apparently increase the toxic effects of spergon, but materially enhance its therapeutic activity. Since they

are oil-in-water emulsions they are easy to apply and assure a satisfactory contact between drug and skin. While such combinations, for instance 50 per cent spergon® in amerchol,® do not cure scalp infection with M. audouini in all cases, the results appear to be definitely better than with other preparations which have been applied directly to the cutaneous surface. Moreover, it has been possible to effect cure when epilation with roentgen rays has failed. Therefore, it appears that this benzoquinone derivative has a definite place in the therapy of infections of this type.

In view of the data presented, it seems "safe" to apply to the unbroken skin an ointment containing 50 per cent tetra-chloro-para-benzoquinone. Probably with caution such a concentration may also be used on excoriated areas. No signs of systemic reaction to this drug have been observed in the present series of cases, and only 1 instance of any such disturbance has been recorded in our entire experience with it.[1]

It may be reemphasized at this point that fungi can apparently build up a tolerance for spergon.® This was especially noted in our first series of experiments[1] in which the same patients received successively increasing concentrations of the drug. Four patients in the present series who were similarly treated showed an equally pronounced tendency toward the same type of response.

We believe that the majority of fungous infections, save infection due to M. audouini, will respond completely to a 10 per cent concentration of spergon® in amerchol.® For the conditions due to M. audouini, it seems wise to use at least a 30 per cent strength in the same medium, with a prompt change to a 50 per cent concentration if no improvement has been observed by the end of one week of treatment.

The optimum medium for administering tetra-chloro-para-benzoquinone—powder or ointment—depends on the purpose for which it is prescribed. In general, however, powders are best suited to areas where moisture will normally be present and ointments to other portions of the body's surface.

SUMMARY AND CONCLUSIONS

Tetra-chloro-para-benzoquinone has been employed in 155 cases of human fungous infections as an ointment in concentrations varying from 5 to 50 per cent. Of 96 patients with infection due to Microsporon audouini, 24, or 25 per cent, were permanently cured. All but 6 of the remainder were improved. Of 39 patients with other types of tinea capitis (exclusive of that due to M. audouini)

24, or 61.6 per cent, were cured, while each of the others was improved. Concentrations of the drug in an ointment base varied from 5 to 50 per cent.

In 1 case each of tinea favus and tinea versicolor there was apparently no improvement effected by treatment with tetra-chloro-para-benzoquinone as a 5 per cent ointment in a wool fat–petrolatum base. The condition in 3 cases of tinea cruris was aggravated by tetra-chloro-para-benzoquinone when used both as an ointment and as a powder. Seven of 11 patients suffering from epidermatophytosis were cured by the use of tetra-chloro-para-benzoquinone as a dusting powder in the shoes and on the lesions; 3 of the remainder were improved; 1 was not helped. It is concluded that spergon* is an effective fungicide, with low toxicity, capable of application in the human being to a wide variety of parasitic cutaneous infections.

STUDY OF ONE HUNDRED AND TWENTY DEATHS OCCURRING IN A DERMATOLOGIC SERVICE

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THE INFREQUENT occurrence of a fatal outcome in diseases seen in the average dermatologic practice has been the subject of a quip which the dermatologist hears almost daily and the substance of which he has long since ceased to deny. While it must be admitted that death from cutaneous diseases is unusual, it is by no means rare. In a recent survey at the Los Angeles County Hospital, it was noted that during the period from July 1, 1940 to July 1, 1946, 120 deaths had occurred in the dermatology and syphilology service. The causes of death in this sizable series, available only in a large general hospital, have been analyzed, and the data are presented in this paper.

MATERIALS AND METHODS

All deaths occurring in the dermatology and syphilology service during the period mentioned were included in the present study. The hospital records of the 120 patients were analyzed in detail, and, when available, data on the following factors were obtained: age, sex, race, past history, history of present illness, physical findings, results of laboratory procedures, antemortem and postmortem diagnoses and treatment. Patients with dermatoses who died in other services of the hospital were not included in this study. Some of the data obtained appear to be of questionable significance, but are presented for the sake of completeness.

DATA

From July 1, 1940 to July 1, 1946, 288,454 patients were admitted to the Los Angeles County Hospital, and 31,195 deaths occurred there. These figures represent an over-all ratio of 9.2 admissions to 1 death. During this same period, there were 5,185 admissions in the dermatology and syphilology service and 120 deaths, a ratio of 43.2 : 1.

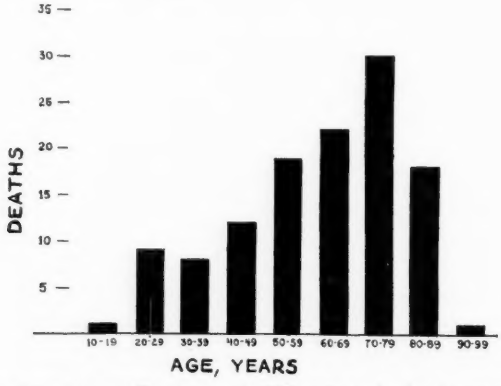
Sex and Age.—Of the 120 deaths, 57 occurred in female and 63 in male patients. The incidence of deaths in various age groups is set forth in the chart.

From the Department of Dermatology and Syphilology, University of Southern California School of Medicine, and the Dermatology and Syphilology Service, Los Angeles County Hospital.

The youngest patient to die was 19 years of age and the oldest 93. The average age at the time of death was 61.4 years.

Race.—One hundred and five patients were of the Caucasian, 13 of the Negro and 2 of the Mongolian race.

Duration of Hospitalization.—The shortest stay in the hospital terminating in death was 4 hours and the longest 1,415 days. The average length of hospitalization was 53.1 days per patient.



Incidence of death according to age in 120 patients in the dermatologic service of Los Angeles County Hospital.

TABLE 1.—*Summary of Antemortem Cutaneous Diagnoses*

	Number of Patients
Pemphigus	25
Exfoliative dermatitis	15
Neoplasms	14
Other types of dermatitis	11
Ulcers due to stasis	11
Herpes zoster	8
Syphilis	6
Coccidioidomycosis	4
Lupus erythematosus disseminatus	3
Cutaneous ulcerations, type undetermined	3
Erythema multiforme	3
Miscellaneous conditions *	17
Total	120

* This includes 2 patients each with psoriasis and pyoderma and 1 patient each with multiple abscesses, actinomycosis, toxic hepatitis due to arsenic, gangrene due to arteriosclerosis, dermatophytosis, dermatitis herpetiformis, herpes gestationis, infectious granuloma (type undetermined), cellulitis of the floor of the mouth (Ludwig's angina), pellagra, periarteritis nodosa, pyoderma gangrenosum and scleroderma.

Antemortem Cutaneous Diagnosis and Immediate Cause of Death.—For the purpose of giving an over-all picture, the clinical, antemortem cutaneous diagnoses are presented in table 1 and the immediate causes of death in table 2.

It will be noted from table 1 that patients with many minor and usually nonfatal dermatoses were included in the series. This was due to the admission to the dermatology service of patients with minor cutaneous diseases who concurrently exhibited more serious diseases of other systems. These patients, if time permitted, were seen in consultation with representatives of the services concerned.

TABLE 2.—*Summary of Immediate Causes of Death* *

	Number of Patients
Bronchopneumonia	38
Cardiac failure (coronary occlusion or congestive heart failure)	25
Pemphigus	12
Uremia	8
Lobar pneumonia	5
Exfoliative dermatitis	4
Coccidioidomycosis	3
Meningitis	3
Mycosis fungoides	3
Miscellaneous †	19
Total	120

* As entered on death certificate, based on clinical diagnosis at time of death or on postmortem examination, if performed.

† This includes 2 patients each with hemorrhage, necrosis of the liver, lupus erythematosus disseminatus, senility and sepsis, and 1 patient each with actinomycosis, anemia, aneurysm (ruptured), cerebral vascular accident, acute hemolytic crisis, intussusception, leukemia cutis (lymphatic), tuberculosis of the lungs and cellulitis of the floor of the mouth (Ludwig's angina).

TABLE 3.—*Cause of Death in 26 Patients with Dermatitis*

Type of Dermatitis and Immediate Cause of Death*	Age, Years
Exfoliative	
Due to arsenic	
Bronchopneumonia	56
Exfoliative dermatitis	47
Exfoliative dermatitis	32
Bronchopneumonia	48
Bronchopneumonia	22
Bronchopneumonia	55
Lobar pneumonia	34
Cardiac failure	34
Bronchopneumonia	22
Due to undetermined cause	
Bronchopneumonia	74
Anemia	46
Bronchopneumonia	45
Bronchopneumonia	68
Cardiac failure	69
Due to sulfonamide drugs	
Cardiac failure	47
Average	46.6

Incidence of various causes	Deaths
Bronchopneumonia	8
Cardiac failure	3
Lobar pneumonia	1
Exfoliative dermatitis	2
Anemia	1
Total	15

Atopic	
Cerebral vascular accident	62
Eczematoid	
Bronchopneumonia	82
Factitia	
Lobar pneumonia	44
Medicamentosa	
Cardiac failure	71
Senile	
Cardiac failure	67
Uremia	93
Toxic	
Cardiac failure	84
Cardiac failure	82
Venenata	
Senility	83
Cardiac failure	64
Bronchopneumonia	63
Average	72.2

Incidence of various causes	Deaths
Cardiac failure	5
Bronchopneumonia	2
Cerebral vascular accident	1
Lobar pneumonia	1
Senility	1
Uremia	1
Total	11

* As entered on death certificate.

Table 2 presents the immediate causes of death in the entire group as entered on the death certificates, based on clinical diagnosis at the time of death or on postmortem examination, if performed. It is noteworthy that pneumonia and cardiac failure accounted for the deaths of 68 patients, or 56.6 per cent of the series. Pemphigus was listed as the immediate cause of death in 12 patients; there were 25 with this disease. The significance of the large number of deaths due to pneumonia will receive attention later in the paper.

In order to study the available data in more detail, the deaths of the 84 patients with the six dermatoses most frequent in this series have been analyzed with respect to age of patients and immediate cause of death, as shown in tables 3 to 7.

TABLE 4.—*Cause of Death in Patients with Pemphigus*

Immediate Cause of Death*	Age, Years
Bronchopneumonia	52
Pemphigus	67
Bronchopneumonia	81
Bronchopneumonia	35
Pemphigus	59
Pemphigus	58
Pemphigus	84
Pemphigus	71
Cardiac failure	32
Pemphigus	82
Pulmonary tuberculosis	65
Pemphigus	33
Pemphigus	70
Pemphigus	58
Bronchopneumonia	73
Bronchopneumonia	92
Bronchopneumonia	86
Bronchopneumonia	75
Cardiac failure	65
Cardiac failure	83
Pemphigus	56
Pemphigus	72
Cardiac failure	78
Pemphigus	26
Bronchopneumonia	50
Average	63.6

Incidence of various causes	Deaths
Pemphigus	12
Bronchopneumonia	8
Cardiac failure	4
Pulmonary tuberculosis	1
Total	25

* As entered on death certificate.

Patients with Dermatitis (table 3): The cases of dermatitis were divided into two categories, those of the exfoliative type and those of various miscellaneous types. The age at death of the patients with exfoliative dermatitis varied from 22 to 74 years, the average age being 46.6 years. Pneumonia was the most frequent immediate cause of death, occurring in 9 of the 15 patients in this group. In the group with nonexfoliative dermatitis the patients ranged in age from 44 to 93 years, the average for the group being 72.2 years. This is in sharp contrast to the average age of 46.6 years in the group with exfoliative dermatitis. It is also noteworthy that pneumonia was listed as the immediate cause of death in only 3 of the 11 cases of nonexfoliative dermatitis, as compared with 9 of 15 cases of exfoliative dermatitis.

Patients with Pemphigus (table 4): The ages of the patients with pemphigus ranged from 26 to 86 years; the average was 63.6 years. Approximately one-half the patients were over 70 years of age. Tabulation of this group according to religion and race revealed 3 patients of Jewish extraction and 22 gentiles, of whom 3 were Negroes and 1 of the Mongolian race.

Patients with Neoplasms (table 5): The ages of these patients ranged from 43 to 81 years. The average was 61.7 years. Pneumonia was the immediate cause of death in one-half the patients in this group.

Patients with Dermatitis Due to Stasis (table 6): The ages of the 11 patients in this group, which includes those with and those without ulceration,

TABLE 5.—*Cause of Death in Patients with Neoplasms*

Type of Neoplasm(s) and Immediate Cause of Death*	Age, Years
Metastatic carcinoma	
Cardiac failure	62
Basal cell carcinoma	
Bronchopneumonia	73
Lymphoblastoma	
Undifferentiated, of the cutis	
Bronchopneumonia	69
Exfoliative dermatitis	81
Bronchopneumonia	63
Mycosis fungoides	
Lobar pneumonia	61
Mycosis fungoides	45
Mycosis fungoides	72
Mycosis fungoides	76
Reticulum cell lymphosarcoma	
Bronchopneumonia	54
Bronchopneumonia	69
Leukemia cutis	
Bronchopneumonia	72
Leukemia cutis	43
Sarcoma	
Intussusception of jejunum	54
Average	61.7

Incidence of various causes	Deaths
Bronchopneumonia	6
Mycosis fungoides	3
Cardiac failure	1
Exfoliative dermatitis	1
Intussusception	1
Leukemia cutis	1
Lobar pneumonia	1
Total	14

* As entered on death certificate.

ranged from 62 to 82 years. The average age was 71.9 years. Cardiac failure was the most frequent immediate cause of death, occurring in 7 persons, while bronchopneumonia occurred in 2. It would appear that in this entire group the dermatoses were only indirectly contributory or coincidental to the ensuing deaths.

Patients with Herpes Zoster (table 7): In this group of 8 patients the ages ranged from 73 to 85 years, the average being 77.7 years. In no instance was the disease herpes of the fatal variety, the immediate cause of death being unrelated, at least directly, to the dermatosis. The advanced age of the patients in this group is of interest.

Patients with Syphilis: There were 6 deaths in patients with syphilis. Three of these had neurosyphilis; 2, cutaneous gummas, and 1, an aortic aneurysm.

The ages varied from 48 to 70 years; the average age was 55.5 years. Immediate causes of death were listed as bronchopneumonia in 2 patients and lobar pneumonia, ruptured aneurysm, uremia and meningitis in 1 patient each.

Histopathologic Examination.—In 49 cases, histopathologic examination of the skin was made ante mortem and/or post mortem. In 24 instances the clinical diagnosis was substantiated by results of the histologic examination, while in 25 the

TABLE 6.—*Cause of Death in Patients with Dermatitis Due to Stasis*

Immediate Cause of Death*	Age, Years
Bronchopneumonia	74
Cardiac failure	73
Bronchopneumonia	67
Cardiac failure	80
Acute hemolytic crisis	62
Cardiac failure	64
Cardiac failure	81
Cardiac failure	56
Cardiac failure	76
Cardiac failure	82
Uremia	76
Average	71.9

Incidence of various causes	Deaths
Cardiac failure	7
Bronchopneumonia	2
Acute hemolytic crisis	1
Uremia	1
Total	11

* As entered on death certificate.

TABLE 7.—*Cause of Death in Patients with Herpes Zoster*

Immediate Cause of Death*	Age, Years
Gastric hemorrhage	74
Uremia	73
Cardiac failure	81
Bronchopneumonia	80
Bronchopneumonia	85
Bronchopneumonia	75
Cardiac failure	75
Cardiac failure	79
Average	77.7

Incidence of various causes	Deaths
Bronchopneumonia	3
Cardiac failure	3
Gastric hemorrhage	1
Uremia	1
Total	8

* As entered on death certificate.

microscopic interpretation was either not conclusive or in disagreement with the clinical diagnosis.

History.—The duration of the dermatoses present at death ranged from four days to twenty-five years. There does not appear to be any significant data obtainable from the study of this factor. The history of other significant diseases in this series, likewise, failed to reveal any data of particular interest.

Of the 120 patients studied, 59 gave a history of some previous cutaneous disease, and 12 stated that they had had syphilis. The history of previous dermatoses was

of no particular significance, even in those patients with cutaneous disease which contributed directly to their death.

Treatment.—As might be supposed, treatment was for the most part nonspecific, consisting mainly of the application of compresses and various ointments, administration of sulfonamide drugs (and, more recently, penicillin), roentgen radiation, high vitamin intake and transfusions. In addition to the dermatologic therapy, treatment was given for the concurrent diseases. Results of therapy for the dermatoses in this series of patients were not, in the main, particularly successful; they were difficult to evaluate. Notes on the charts of 38 patients indicated that the lesions had showed improvement, but those for 62 patients indicated failure to respond to dermatologic therapy. In 7 cases, the results were questionable. Thirteen patients received no treatment for their dermatoses, either because of too short a stay in the hospital or because only palliative measures were indicated.

There were 6 patients who presented complications of dermatologic therapy (table 8). All these complications were reactions to treatment, there being 2 instances of leukopenia due to sulfonamide drugs, 1 reaction resulting from the use of iodine and 1 from the use of mercury and potassium iodide, an acute hemolytic crisis due to a transfusion and necrosis of the liver due to malaria therapy.

TABLE 8.—*Complications Due to Dermatologic Therapy in 6 Patients*

Complication	Type of Therapy	Clinical Diagnosis
Leukopenia	Sulfonamide drugs	Mycotic ulceration
Leukopenia	Sulfonamide drugs	Lupus erythematosus
Severe exacerbation	Iodine	Pyoderma gangrenosum
Acute hemolytic crisis	Blood transfusion	Ulcers due to stasis (anemia)
Necrosis of the liver	Malaria	Syphilis of central nervous system
Glossitis	Mercury and potassium iodide	Syphilis of central nervous system

Bed Rest.—Of the 120 patients, complete bed rest was ordered for 93 and partial bed rest for 25; orders for the remaining 2 were undetermined. It is probable that a number of the group for whom complete bed rest was ordered took bathroom privileges, although their charts did not so indicate. Thirty-two of the 93 patients confined to their beds died of bronchopneumonia, while 6 of the 25 ambulatory patients died of the same cause.

Blood Picture.—Complete studies of the blood showed that 34 of the patients had anemia of some type; 3, polycythemia; 29, leukocytosis, and 12, leukopenia. Eosinophilia was present in 12 instances. No apparent correlation was observed between the blood picture and the dermatoses. The blood pictures of the patients with lymphoblastomas and related conditions were varied and for the most part nondiagnostic. Biopsies performed on the bone marrow in several of the patients with lymphoblastomas were not diagnostic.

Blood Chemistry.—Some type of blood chemistry studies were made for a total of 81 patients. A detailed analysis of the group with pemphigus revealed the following: Of the 25 patients, blood chemistry studies were made for 23. Concentration of chlorides, reported as sodium chlorides, was determined in 13 patients, in 10 of whom it was normal and in 3 decreased. The albumin-globulin ratio was determined for 20 patients and was abnormal for all; albumin was decreased in all 20, while globulin was increased in 4 and decreased in 1. The amount of serum phosphorus was normal in 2 patients and increased in 1. The quantity of blood calcium was determined for 12 patients; it was normal in 11 and decreased in 1. Nonprotein nitrogen was determined in 14 patients with pemphigus, being normal

in 11 and increased in 3. In 4 of the 5 specimens of blood in which the amount of creatinine was determined, values were above normal.

A similar analysis of the 15 patients with exfoliative dermatitis showed that 10 had disturbances of the albumin-globulin ratio. As in the group with pemphigus, albumin was decreased in all instances. Of 8 determinations of nonprotein nitrogen, 7 were within normal limits and 1 was elevated.

Blood Cultures.—Blood cultures were made for 11 patients. For 7 the cultures yielded pathogens, and for 4 the cultures were sterile. Two of the cultures were made post mortem; they yielded pathogenic organisms. Because of the small series, the types of organisms recovered are not significant.

Serologic Tests of the Blood for Syphilis.—Serologic tests for syphilis were made on 97 patients; the reactions of 77 were negative, of 14 positive and of 6 doubtful. Of the 6 patients for whom the principal diagnosis was syphilis, 4 were seropositive while 2 were seronegative.

Sedimentation rates were determined on very few patients and hence are omitted from the presentation.

Examination of the Urine.—Urinalysis for the most part revealed nothing significant. Thirty-two patients had albuminuria, and 22 had additional abnormal material present, such as casts or red and white blood cells. There was apparently

TABLE 9.—*Comparison of Antemortem and Postmortem Diagnosis in 5 Deaths*

Antemortem Diagnosis	Postmortem Diagnosis
Pyoderma gangrenosum	Mycosis of the spleen with ulceration of the skin
Ulceration of skin	Syphilis of the lungs
Exfoliative dermatitis (due to drug or scarlet fever)	Hodgkin's disease
Dermatitis factitia	Gangrene (amputation of fingers)
	Carcinoma of the pituitary gland
Herpes zoster with encephalitis	Uremia; herpes facialis

no relation between the type of dermatosis and the results of urinalysis to warrant further comment. Special examinations of the urine for arsenic, iodides and bromides were made in a small number of cases.

Miscellaneous Examinations.—In 29 cases smears and cultures of the skin and mucous membranes were made, and various results were obtained. Roentgenologic studies revealed nothing significant from a dermatologic viewpoint. Special laboratory studies were made when indicated, but the results are not of interest in this study.

Postmortem Examinations.—Of the 120 cases resulting in death studied, postmortem examination was performed in 53, or 44.1 per cent. Postmortem examinations were performed in 34.7 per cent of the cases resulting in death for the entire hospital during this period. Of the 53 autopsies performed, the postmortem diagnosis in 5 instances failed to substantiate the antemortem clinical dermatologic diagnosis. The antemortem and postmortem diagnoses in these cases are set forth in table 9.

COMMENT

The average age of 61.4 years in this series is rather surprising, particularly in view of the fact that these patients were of an economic stratum of society in which the life expectancy is well below this figure. In comparison, the average age at death of 3,952 patients on medical

services other than that of dermatology in 1943-1944 was 54.8 years. The average age of 63.6 years at death of the patients with pemphigus, one of the few traditionally fatal dermatoses, is of great interest. Since this is a rather large series of deaths of patients with pemphigus, one may conclude that while pemphigus is usually a fatal disease it is also a disease of old age. Actually, the average age at death of these patients is practically the normal life expectancy for the entire population of the United States. This would suggest that the etiology of pemphigus is degenerative, rather than infectious.

In contrast were the 15 deaths in patients with exfoliative dermatitis; the average age of these patients at death was 46.6 years. In the group of 8 patients with herpes zoster, the average age at death was 77.7 years. While herpes zoster was not the direct cause of death in these patients, it must be considered a serious disease in the aged, as bronchopneumonia developed as a complication in 3 patients.

Sex seemed to be of little significance as a predisposing factor in any of the dermatoses terminating fatally. The racial factor was also apparently unimportant, even in pemphigus. In this group, contrary to expectations, only 3 of 25 patients were of Jewish extraction.

The average length of hospitalization was 53.1 days per patient; the periods varied from 4 hours to 1,415 days. Actually, the majority of these patients, particularly those with only cutaneous diseases, could have been cared for at home had the economic situation permitted. In view of the average cost of hospitalization today and the scarcity of hospital beds, it would seem advisable to care for these patients at rest homes or in other facilities. It should be borne in mind that once these patients are admitted, frequently for diagnostic study only, it may be impossible to discharge them because of socioeconomic reasons.

For the most part the immediate causes of death were of a nondermatologic nature, although the cutaneous disease present may in many instances have been a significant contributing factor. This is particularly true of the 43 patients dying of bronchopneumonia and lobar pneumonia. Although many of these persons were of advanced age, in which pneumonia is frequently the terminal event, this is a significantly high incidence, probably brought about by the bed rest utilized therapeutically for their dermatoses. These data would seem to indicate that bed rest should not be prescribed for older patients with cutaneous diseases except when absolutely necessary. Indeed, in these patients active prophylactic measures against the various types of pneumonia are strongly indicated.

It appears important and is in conformity with previously recorded experience that 9 of 15 patients in the group with exfoliative dermatitis died of pneumonia. All these patients were given complete bed rest, and most of them were relatively young adults, who do not ordinarily die

of pneumonia. While it is recognized that the disturbances of temperature present in exfoliative erythroderma predispose the patient to pulmonary complications and that the exfoliative process may extend to the bronchial tree, active prophylactic measures should be taken against pneumonia in these patients.

It is of interest that in the deaths of this series which were directly attributable to dermatologic diseases, namely, pemphigus, neoplasms and the exfoliative dermatitides, treatment was of little value. These data emphasize the nonspecific nature and ineffectiveness of therapy in serious dermatologic diseases.

For this group of 120 patients, hundreds of laboratory procedures were performed which for the most part were not contributory to the successful management of the patients. This represents a sizable expenditure of funds. It indicates a need for better understanding of which laboratory procedures may be of value in the treatment of a patient with dermatosis, and, even more important, a need for recognition of those tests which will be noncontributory regardless of the results obtained.

SUMMARY

The records of 120 patients who died in the dermatology service of a large general hospital over a six year period have been analyzed and reported.

About one-half these patients presented cutaneous diseases usually considered likely to terminate in death; the remainder were patients with serious systemic disease, admitted to the dermatology service because of minor cutaneous lesions.

Longevity was not significantly affected by the cutaneous diseases occurring in this group of patients, as evidenced by the average age of 61.4 years at the time of death.

Sex was not a significant predisposing factor, there being 63 male and 57 female patients in the series.

Pemphigus was the most frequently occurring dermatosis in this group of patients; there were 25 persons with this disease. Next in frequency were exfoliative dermatitis (15 patients) and neoplasms (14 patients).

Bronchopneumonia and cardiac failure were the most frequently listed immediate causes of death, occurring in 38 and 25 instances respectively. The incidence of pneumonia in patients with exfoliative dermatitis was significantly higher than in patients with nonexfoliative dermatitis.

Of the 25 patients with conditions diagnosed as pemphigus, only 3 were of Jewish extraction, while 22 were gentiles. This is not in accord

with the generally accepted belief that pemphigus occurs most frequently in persons of Jewish descent.

Bed rest, partial or complete, is not without danger as a therapeutic measure, as indicated by the high incidence of pneumonia (43 patients). The advisability of prophylactic measures against this complication is apparent from this study.

Many patients, admitted to the dermatology service for administrative reasons rather than for urgently needed hospital care of their dermatoses, remained for economic reasons in the hospital until death. The socioeconomic disadvantages of the waste of space and funds of this procedure are discussed.

Treatment of dermatoses likely to terminate in death was nonspecific and ineffective for the most part.

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Clinical Notes

MULTIPLE CUTANEOUS EFFECTS OF POTASSIUM SULFOCYANATE

Report of a Case

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In 1903 Pauli suggested the use of sodium or potassium sulfocyanate in the treatment of hypertension. Since then, several observers (including Baker and Brunsting,[1] in 1937; Wald, Lindberg and Barker,[2] in 1939; Barker, Lindberg and Wald,[3] in 1941; Russell and Stahl,[4] in 1942; Forster,[5] in 1943; Petersen,[6] in 1943; Rawson, Hertz and Means,[7] in the same year; Koffler and Freireich,[8] in 1944; Hines,[9] in 1946) have warned of toxic effects which may be caused by these drugs. As a matter of fact, in 1929,[10] and again in 1942,[11] the Council on Pharmacy and Chemistry of the American Medical Association condemned the use of the cyanates.

1. Baker, T. W., and Brunsting, L. A.: Dermatitis Medicamentosa Resulting from Administration of Sulfocyanates in Treatment of Hypertension, J. A. M. A. **108**:549-550 (Feb. 13) 1937.

2. Wald, M. H.; Lindberg, H. A., and Barker, M. H.: Toxic Manifestations of Thiocyanates, J. A. M. A. **112**:1120-1124 (March 25) 1939.

3. Barker, M. H.; Lindberg, H. A., and Wald, M. H.: Further Experiences with Thiocyanates: Clinical and Experimental Observations, J. A. M. A. **117**: 1591-1594 (Nov.) 1941.

4. Russell, W. O., and Stahl, W. C.: Fatal Poisoning from Potassium Thiocyanate Treatment of Hypertension: Report of Case and Review of Literature, J. A. M. A. **119**:1177-1181 (Aug. 8) 1942.

5. Forster, R. E., II: Am. J. M. Sc. **206**:668-676 (Nov.) 1943.

6. Petersen, D. M.: J. Missouri M. A. **40**:279-281 (Sept.) 1943.

7. Rawson, W. R.; Hertz, S., and Means, J. H.: Ann. Int. Med. **19**:829-842 (Dec.) 1943.

8. Koffler, A., and Freireich, A. W.: Am. J. M. Sc. **207**:374-376 (March) 1944.

9. Hines, E. A., Jr.: M. Clin. North America **30**:869-877 (July) 1946.

10. Elixir Kacyan Mc Neil and Tablets Kacyan Mc Neil Not Acceptable for N. N. R., report of the Council on Pharmacy and Chemistry, J. A. M. A. **92**:1838 (June 1) 1929.

11. Goldblatt, H.; Kahn, J. R., and Lewis, H. A.: Studies on Experimental Hypertension: Experimental Observations on the Treatment of Hypertension, report of the Council on Pharmacy and Chemistry, J. A. M. A. **119**:1192-1201 (Aug. 8) 1942.

REPORT OF CASE

Mrs. C. C. an American housewife aged 50, was placed under treatment with potassium sulfocyanate in January 1947, because of severe hypertensive disease. The daily dose was started at 3 grains (0.195 Gm.) and was slowly increased to 9 grains (0.585 Gm.). Readings of the drug level in the blood, taken at regular intervals, ranged from 2.1 to 8 mg. per hundred cubic centimeters, reaching the latter level only during the sixth week. At the end of this time, the patient complained of fatigue, lethargy, a feeling of extreme heaviness and difficulty in getting about. As the patient had previously and frequently complained of tiredness and exhaustion, some of her symptoms were discounted; but in spite of this consideration the potassium sulfocyanate was discontinued.

After a lapse of four weeks, the potassium sulfocyanate therapy was recommenced. The daily dose was started at 2 grains (0.13 Gm.) and later increased to 3 grains (0.195 Gm.) and then to 4 grains (0.26 Gm.). The total time of therapy did not exceed two weeks. The drug was discontinued because three peculiar symptoms developed: (1) frontoparietal loss of hair, (2) soreness of the mouth and (3) perianal pruritis.

Examination on Aug. 1, 1947, revealed the following condition: 1. Considerable loss of hair over the frontal and parietal areas. With slight traction, such as that produced by running the fingers through the hair, a large number of hair shafts (twenty-five or more) were easily removed from the scalp. This severe loss of hair was not demonstrable over the occipital areas. The hair shafts were atrophic, dry and lifeless, and their follicular ends were devoid of the usual moist, cat-of-nine-tails appearance. Most of the patient's hair was yellow and discolored from an ointment which had been ordered for her by a physician, supposedly to stop the fall of hair.

The scalp itself presented nothing unusual except that it was totally devoid of short hair and had a smooth and shiny (typically bald) appearance, due to the complete collapse of the follicular openings. No adventitious signs of inflammation or hemorrhage were seen.

2. The mucous membrane covering the alveolar process over the upper incisors, the area of soreness of which the patient complained, presented pinpoint hemorrhages; we counted about eighteen blood-stained macules. There was absence of any form of gingivitis, and the rest of the mucous membrane of the oral cavity was unaffected. The soreness of which the patient complained was peculiar, as it was caused by bite pressure rather than by pressure exerted on the area by the petechial hemorrhages. There was no bleeding after use of the toothbrush.

3. In the perianal area, and extending over the perineum in the area between the anus and the vagina, a dermatitis was present. Excoriations caused by scratching and a deep linear fissure, located centrally, were evident. The skin was thickened and dark red; the itching was intense. None of these symptoms were present before the second administration of the sulfocyanate.

COMMENT

The skin and its appendages were an excellent index to the toxic effect of this drug, as it is in many other conditions and to many other drugs. The sensory, the neurologic and the dermatologic symptoms of the toxic effects were not unlike those produced by overdoses of thallium acetate, particularly with respect to our own patient's experience with the toxic loss of hair. As in the intoxication referred to, the symptoms persist for a long period, and simple withdrawal of the drug is not followed immediately by the complete disappearance of them.

CONCLUSION

Potassium sulfocyanate, which on so many other occasions has been pointed out as a dangerous drug, may cause toxic symptoms which lead to (1) a rapid, toxic fall of hair, (2) petechial hemorrhages of the mucous membrane of the alveolar processes, without accompanying stomatitis, and (3) persistent, pruriginous, residual dermatitis of the perineum and perianal areas.

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HYALURONIC ACID-HYALURONIDASE ENZYME SYSTEM IN PEMPHIGUS

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In many patients with pemphigus the epidermis, even in those areas of skin where bullae have not appeared, may be easily displaced from the underlying dermis by gentle friction (Nikolsky's sign). The reason for this manifestation would appear to be a general defect in the cement substance of the skin. The highly viscous mucopolysaccharide hyaluronic acid has been shown to be a constituent of the cement substance of normal skin. Furthermore, it is known that hyaluronic acid is readily hydrolyzed by the enzyme hyaluronidase. MacCardle and associates [1] suggested that bullae might be formed in localities where hyaluronic acid had been destroyed by enzymatic hydrolysis. Although no direct studies of this enzyme system were undertaken by these authors, data compatible with their hypothesis were furnished by observations on the comparative rates of spread of hemoglobin injected into the skin of normal subjects and of patients with pemphigus.

In the present study, further investigation of this enzyme system was carried out on 3 patients with pemphigus. All 3 demonstrated Nikolsky's sign. Two of the patients died during the active stage of the disease, and the third died of an intercurrent infection during a period of remission.

EXPERIMENTAL INVESTIGATION

Our experimental studies were directed along two lines: (1) an attempt to demonstrate hyaluronidase activity in the serum, bulla fluid and extracts of the skin of patients with pemphigus, and (2) comparative assays of the amount of hyaluronic acid present in normal skin and in the skin of patients with pemphigus.

1. Hyaluronic acid, to be used as a substrate for the demonstration of hyaluronidase activity, was prepared from fresh human umbilical cords by a slight modification of the method described by Haas.[2] Hyaluronidase activity was assayed

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1. MacCardle, R. C.; Baumberger, J. P., and Herold, W. C.: Histochemistry of Pemphigus Lesions, with Special Reference to Bullous Formation, Arch. Dermat. & Syph. **47**:517 (April) 1943.

2. Haas, E.: On the Mechanism of Invasion: I. Antinvasin I, an Enzyme in Plasma, J. Biol. Chem. **163**:63 (April) 1946.

by measuring, in an Ostwald viscosimeter, the decrease in viscosity of a test solution of hyaluronic acid as a result of depolymerization by the enzyme.

As a preliminary control to demonstrate the efficacy of the methods employed, a preparation of active hyaluronidase was made from a twelve hour culture in broth of a virulent strain of Staphylococcus aureus. With this solution there was prompt depolymerization of hyaluronic acid, readily demonstrable by a prompt decline in viscosity. Analogous studies were then carried out with the substitution of serum, fresh sterile bulla fluid or extracts of the skin of patients with pemphigus in place of the known hyaluronidase solution. In no instance could depolymerization of hyaluronic acid be demonstrated in terms of a detectable decrease in viscosity.

2. Acid hydrolysis of hyaluronic acid yields reducing sugars which can be readily measured and thus serves as a method of assay of the original mucopolysaccharide. Preliminary studies were made to establish conditions of hydrolysis and of measurement of reducing power of the liberated sugar which would give constant results when applied to solutions of the hyaluronic acid prepared from umbilical cords. The same analytic procedures were then applied to extracts of (*a*) normal skin and (*b*) skin from the 3 patients with pemphigus. These extracts were prepared from skin removed at autopsy soon after death. The skin was removed in its whole thickness, freed of subcutaneous fat by careful dissection and then homogenized in a buffer solution at p_H 7.4. The resulting suspensions of finely divided skin were stored at low temperature for several days and then centrifuged, and the supernatant liquid was used for chemical study. While acid hydrolysis of all these extracts produced a slight but measurable increase in reducing material, there was no significant difference in the results obtained with extracts prepared from the normal and from the abnormal skins.

As a result of these studies, we are forced to conclude that, with the admittedly crude methods employed, no evidence was obtained which would indicate that in pemphigus there is either an excessive amount of hyaluronidase or a deficiency of hyaluronic acid to account for the pathologic changes exhibited in the skin.

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PITYRIASIS ROSEA

Report of Three Cases Within One Household

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Although the causative agent in pityriasis rosea remains obscure, occasional reports of cases of this disease in husband and wife and in other members of one family have suggested that it is, as Andrews [1] stated, "feebly infectious." The 3 cases reported here substantiate this view. It is of particular interest that the second patient was not a member of the household of the other 2, but was visiting their home when the disease was apparently contracted.

REPORT OF CASES

CASE 1.—E. C., a girl aged 10 years, was seen on Nov. 5, 1946, with widespread typical pityriasis rosea of two weeks' duration. The eruption involved the entire

From the Pittsburgh Skin and Cancer Foundation.

1. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946.

trunk, with new lesions appearing on the proximal portions of the arms and thighs. The only symptom was mild itching. The eruption had almost disappeared on November 20, after four exposures to ultraviolet radiation at three to six day intervals. Treatment of a few recurrent lesions on December 20 and 26 resulted in the complete clearing of the eruption.

CASE 2.—Mrs. P. C., aged 51, was seen on March 25, 1947, with widely disseminated pityriasis rosea of the trunk and extremities, of one week's duration. A large lesion on the right ankle was the original herald patch, and the spreading eruption involved the entire body, being most profuse on the trunk. For the past month the patient had been visiting the home of E. C. (case 1). The eruption cleared completely after three exposures to ultraviolet radiation at four day intervals, the last treatment being given on April 4, 1947.

CASE 3.—L. C., a girl aged 4½ years, sister of E. C. (case 1), was seen on April 24, 1947, with a typical lesion of pityriasis rosea, of one week's duration, on the upper portion of the right thigh. A few small, but typical, lesions had appeared on the lower part of the abdomen during the previous two days. This limited eruption promptly subsided after one treatment with ultraviolet radiation.

COMMENT

It is improbable that the disease spread directly from the first patient to the second, since there was an interval of approximately three months between the appearance of the eruptions. Another interval, of one month, existed between the appearance of the eruptions in cases 2 and 3. This might be explained, of course, by a prolonged incubation period.

None of the patients slept together, and the only apparent factor in common is that for a time they lived together in the same house.

CONTACT DERMATITIS DUE TO THE MERCURY OF AMALGAM DENTAL FILLINGS

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The rarity of case reports of contact dermatitis due to the mercury of amalgam dental fillings has prompted us to report 2 cases which we have recently observed. Traub and Holmes [1] reported 2 cases with an extensive review of the literature in 1938, and Blumenthal and Jaffe [2] recorded a similar case in 1929. Ellis and Robinson [3] reported on cutaneous sensitivity to mercurial compounds in 1942. The

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1. Traub, E. F., and Holmes, R. H.: Dermatitis and Stomatitis from the Mercury of Amalgam Fillings, Arch. Dermat. & Syph. **38**:349 (Sept.) 1938.

2. Blumenthal, F., and Jaffe, K.: Amalgamplomben als Ursache von Quecksilberdermatitis, Deutsche med. Wchnschr. **55**:1720 (Oct.) 1929.

3. Ellis, F. A., and Robinson, H. M., Jr.: Cutaneous Sensitivity to Merthiolate and Other Mercurial Compounds, Arch. Dermat. & Syph. **46**:425 (Sept.) 1942.

latter report suggested that sensitivity to mercury or mercurials may be selective, i. e., a patient may be sensitive to complex organic mercury compounds and not to inorganic compounds, and vice versa.

The usual procedure in the preparation of an amalgam filling is as follows: The required amounts of silver alloy (which contains small amounts of copper, zinc and tin) and mercury are triturated together in a mortar. After the mass has been thoroughly mixed it is emptied into the dentist's hands, where it is kneaded in order to express the excess of metallic mercury. Instruments are then used to apply this compound to the cavity. This demonstrates the fact mentioned by Traub and Holmes [1] that particles of mercury are invariably present on the dentist's hands after he has completed the preparation of the compound.

REPORT OF CASES

CASE 1.—E. I., a 14 year old white girl, was first seen in December 1945 because of severe dermatitis about the face, neck and chin. The appearance of this eruption had been noted by her mother to occur whenever the patient had any teeth filled. This train of events occurred after visits to each of several dentists. The eruption was always confined to the skin about the mouth, chin and neck. The past history did not reveal any serious illnesses, but she had had several attacks of rhus dermatitis to which her sensitivity was proved by patch tests. There was no history of sensitivity to mercury.

Examination.—There was an irregular bright pinkish edematous lesion almost entirely encircling the mouth and extending onto the right cheek. Throughout this lesion there were numerous, small, discrete and confluent vesicles. On the neck there were several smaller lesions some of which formed linear groups.

The following items were used in patch tests and the reactions read in forty-eight hours: (1) metallic mercury, with a positive reaction with bleb formation; (2) mercury amalgam, with a positive reaction with bleb formation; (3) silver alloy, with a negative reaction, and (4) the dentist's towel, with a positive reaction with edema and vesiculation. A similar, but unused, towel was procured from the dentist's office, but was not handled by him. The result of a patch test with this was negative in forty-eight hours.

CASE 2.—M. S., a 16 year old white girl, was first seen in January 1947 because of an itching eruption on the chin and anterior part of the neck, which appeared twenty-four hours after visiting a dentist to have fillings inserted. The eruption consisted of ill defined patches of erythema. This subsided within a few days, but on the next visit to the dentist, for the same purpose, a similar eruption appeared in the same areas within twenty-four hours. The patient had a past history of sensitivity to mercury extending over a period of ten years. The last episode of mercurial dermatitis occurred five years previously after the use of ammoniated mercury ointment.

Examination.—There was a pinkish edematous ill defined eruption involving the chin and anterior portion of the neck. The following items were used in patch tests and the reactions read in forty-eight hours: (1) metallic mercury, with a positive reaction with edema, erythema and vesiculation, and (2) mercury amalgam, with a positive reaction with edema, erythema and vesiculation. Severe edematous vesicular dermatitis appeared on the arm where the tests were made, beginning forty-eight hours after the patches had been removed, and spread to involve the entire arm and axilla. This eruption lasted one week.

SUMMARY AND CONCLUSIONS

Two cases of contact dermatitis from use of mercury amalgam fillings are described. The dermatitis in both instances was confined to the perioral area, face and neck. Patch tests to metallic mercury, fresh mercury amalgam and silver alloy were done. Positive reactions to patch tests were observed only to mercury and the mercury amalgam. In such patients, recourse must be had to the use of gold or cement fillings, as mercury is definitely contraindicated.

SEVERE REACTION RESEMBLING THERAPEUTIC SHOCK IN LEPERS FOLLOWING ADMINISTRATION OF "DIASONE"

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AND

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SAN SALVADOR, EL SALVADOR, CENTRAL AMERICA

In the treatment of syphilis with arsenicals and heavy metals, the therapeutic shock, or so-called Jarisch-Herxheimer reaction, has been observed, and we have noted the same type of reaction in 2 lepers with the lepromatous type of the disease who were being treated with "diasone" (disodium formaldehyde sulfoxylate diaminodiphenylsulfone).

This drug, newly adopted in the therapeutics of leprosy, is given credit for the encouraging results we have been achieving. We have had the opportunity to study one of the first cases of this reaction to occur with the application of this drug.

Pfuetze and Pyla [1] reported a case of a severe reaction of the pemphigoid type observed in a tuberculous patient under treatment with "diasone." The pemphigoid eruption was followed by exfoliating dermatitis. Muir,[2] reporting on his treatment of 12 lepers with "diasone," did not refer to any reaction resulting from the application of this drug. At the Pan-American Conference on Leprosy held in Rio de Janeiro in October 1946, no reactions of this nature were reported except the usual ones, such as vomiting, diarrhea, allergic dermatitis, anemia and leukopenia. Souza Lima, of Brazil, in a series of 600 patients treated with "diasone" at the Padre Bento Sanatorium, São Paulo, reported no reaction similar to that under study in our 2 cases.

We know of no other report in connection with this subject; for this reason, and since "diasone" is one of the powerful weapons against leprosy used in modern practice, we consider it important to bring this phenomenon to light.

REPORT OF CASES

CASE 1.—J. H., a man aged 39, a half-breed, when first seen on May 3, 1945, presented nodules on his ear lobes, a papular eruption over nearly his entire

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From the Department of Dermatology and Syphilology, Hospital Rosales.

1. Pfuetze, K. H., and Pyla, M. M.: Severe Reaction Following Administration of Diasone, J. A. M. A. **125**:354 (June 3) 1944.

2. Muir, E.: Diasone in Treatment of Leprosy, Leprosy Rev. **17**:87 (Oct.) 1946.

body, alopecia of the eyebrows and a deformity of the nose, giving him a leonine appearance. There were disturbances in the sensibility of the upper and lower limbs, consisting in complete anesthesia, both superficial and deep, to heat and physical pain. The ulnar nerves were enlarged, and his hands had an edematous appearance.

The Mitsuda test gave a negative reaction on two occasions, but the Hansen bacillus was present in the nasal secretion. The disease was diagnosed as lepromatous leprosy, of the nervous and cutaneous type, Lc3n2.[3]

CASE 2.—V. M., an Indian boy aged 12, when first seen, on April 2, 1946, showed a nodular eruption which partially covered his chin and nose and the gluteal region. These nodules of the multiform type were also located on his ears, deforming them considerably. The patient also had complete loss of sensibility in areas affected by the nodules.

The Mitsuda test twice gave a negative reaction. However, histopathologic study revealed the presence of the Hansen bacillus in the nodules.

The disease was diagnosed as lepromatous leprosy, Lc3n1.

REACTION TO "DIASONE."—At the time these patients entered our dermatologic ward, we first treated them with chaulmoogra oil for several months; later, we changed the treatment to injections of "promin" (sodium-P,P′-diaminodiphenylsulfone-N,N′-didextrose sulfonate). The results obtained from every application were encouraging. The nodular eruption disappeared almost entirely with this treatment.

In May 1947 we began using "diasone" with all our patients, administering a daily dose of 0.30 Gm., given three times a day by mouth. After eight weeks of treatment with this drug, the 2 patients reported here began to complain that the eruption they had formerly had was again breaking out. On close examination, we found the presence of nodules of various sizes, which were rosy and spread over exactly the same areas that they had previously covered at the time the patient entered the hospital. This eruptive phase was accompanied with migraine, epiphora, nausea and fever, the temperature fluctuating between 37.2 and 38.4 C. (98.96 and 101.1 F). Use of the "diasone" was suspended, and the phenomenon gradually disappeared within three days. The total dose of "diasone" given when the reaction occurred was 15.1 Gm. for patient 1 and 10.4 Gm. for patient 2.

SUMMARY

To the known reactions produced by "diasone," such as vomiting, diarrhea and allergic dermatitis, there should be added this toxic effect which we compare to the so-called Jarisch-Herxheimer reaction.

In case 1, as a matter of study, and two weeks after the reaction to the "diasone" had disappeared, we again began to use "diasone," with the result that four days later the eruption reappeared with greater intensity. The time required for the dermatosis to disappear was then lengthened. Consequently, the procedure to be followed in cases of such a reaction should be complete discontinuation of the "diasone."

Hospital Rosales.

3. The numerals indicate the grade of severity of the cutaneous and neural diseases, respectively.

News and Comment

GENERAL NEWS

Second Conference on Tropical Dermatology.—Through the efforts of the Sociedad Mexicana de Dermatologia, and Dr. Fernando Latapi, a second conference in tropical dermatology was arranged and held in Mexico City, Aug. 15-28, 1948. The subjects included: (1) pinta, (2) onchocerciasis, (3) leprosy, (4) leishmaniasis, (5) rhinoscleroma, (6) deep mycoses, (7) parasitic animal infestations and (8) dermatologic aspect of the chemical control of insects.

In addition, there were two meetings of the Mexican Society of Dermatology, with case presentations of the bismuth therapy of vitiligo, calciferol therapy of extensive lupus vulgaris in a child 9½ months old, 2 cases of congenital ichthyosiform erythroderma, melanosis calorica, extensive urticaria pigmentosa, carotinoderma, probable parapsoriasis, probable pityriasis rubra pilaris and the effect of the diazone therapy of extensive mycetoma and malignant melanoma.

The following papers were presented: "Lymphopathia Venerea in Mexico," Dr. Oswaldo Arias; "Dermatitis Vegetans Tropicalis," Dr. Esteban Reyes; "The Concept of Lymphoblastoma," Dr. Julio Bejarano; "Nitrogen Mustard Therapy of Mycosis Fungoides," Dr. Leon Goldman, and "Action of Bismuth on the Buccal Mucosa," Dr. Fermin Raygadas.

Certificates for completion of the conference were given to: Dr. Paul Fasal, San Francisco; Dr. Irene Neuhauser, Chicago; Dr. Marquis R. Huffman, Milford, Mich.; Dr. Frank Leone, New York; Dr. Leslie Nicholas, Philadelphia; Dr. L. J. Owen, Lincoln, Neb.; Dr. Leslie Smith, El Paso, Texas, and Dr. Morris Waisman, Tampa, Fla.

It is intended to repeat the conference, probably in 1950. Those who have attended the previous conferences may have an opportunity for special investigative work in such diseases as leprosy, deep mycoses and pinta, either at the Department of Dermatology at the Hospital General or at the Institute of Tropical Diseases, the Out-Patient Dispensary for Leprosy, the leprosarium or in actual studies in the field.

American Board of Dermatology and Syphilology.—At a meeting of the American Board of Dermatology and Syphilology in Philadelphia, April 2 and 3, 1948, the following candidates were successful and may now be referred to as diplomates of this board: Harold Leon Adler, New York; William C. Boggs, Wheeling, W. Va.; Harold Newton Cole Jr., Cleveland; Charles S. D'Avanzo, Springfield, Mass.; Alfred J. Ephraim, Brooklyn; Lawrence Frank, Brooklyn; John Lewis Fromer, Chestnut Hill, Mass.; Marvin B. Goldstein, Youngstown, Ohio; William B. Guy, Pittsburgh; Alvie B. Harrison, Wichita, Kansas; Eldred B. Heisel, Columbus, Ohio; Franz Herrmann, New York; Jules Maurice Key, San Francisco; Joseph A. Maffongelli, Paterson, N. J.; Samuel Frederick Rosen, Savannah, Ga.; William M. Siskind, Bronx, N. Y.; Adolph S. Sternberg, New York; Kenneth Leslie Stout, Beverly Hills, Calif., and Jacob Saltzman, Waterbury, Conn.

The following candidates were also successful and will be diplomates as soon as they have spent five years in the specialty: Milton H. Applbaum, Philadelphia; Samuel Ayres III, Los Angeles; Saul R. Bergad, Pittsburgh; Harvey Blank, Philadelphia; Donald Boersma, Grand Rapids, Mich.; Beatrice Kalish, Brooklyn; Cyrus W. Loo, Charlottesville, Va.; Robert Morrow McKee, Beaver, Pa.; R. Gordon MacDonald, Riverside, Calif.; Margaret G. Mahoney, Drexel Hill, Pa.; Stanton B. May, Glendale, Calif.; Henry Gordon Morgan, New York; Ralph L. Parker, Bridgeport, Conn.; Daniel J. Perry, Philadelphia; Victor Manuel Rivera, New York, and John Morris Siegel, Lebanon, Pa.

At the meeting of the Board in Ann Arbor, Mich., Oct. 22-24, 1948, the following candidates were certified by the Board and may now be referred to as certified specialists: Maurice A. Belson, New York; Jack H. Bowen, Jacksonville, Fla.; Matthew J. Brunner, Chicago; Robert E. Burns, Victoria, British Columbia, Canada; Robert G. Carney, Iowa City; Lionel M. Cole, Pittsfield, Mass.; Ralph B. Coomber, Santa Ana, Calif.; Maurice T. Fliegelman, Louisville, Ky.; Reuben Goodman, Washington, D. C.; Jacob L. Grund, Brookline, Mass.; Raymond P. Hughes, Washington, D. C.; Evan B. Hume, Philadelphia; Louis G. Jekel, Phoenix, Ariz.; Julius H. Katz, New York; William E. Kelley, Omaha; Vera H. Leaf, Chicago; Norman E. Levan, Los Angeles; Richard C. Light, Nashville, Tenn.; Charles S. Lincoln Jr., Berkeley, Calif.; William C. Marsh, Yeadon, Calif. George W. Miller, Ambridge, Pa.; Joseph I. Mirovich, Los Angeles; Mildred Mumby, Seattle; Paul L. Rentiers, Edmonton, Alberta, Canada; Milton Robin, Chicago; George K. Rogers, Phoenix, Ariz.; Leonard E. Savitt, Los Angeles; Reuben Schwartz, Philadelphia; Hilliard M. Shair, Yonkers, N. Y.; Irving Shapiro, Newark, N. J.; John J. Shaw, Newark, N. J.; Charles Sheard Jr., New York; Harry Sigel, New Haven, Conn.; Joseph I. Singer, Bay Shore, L. I., N. Y.; Seymour J. White, Lawrence, Mass.; James S. Wilkinson, Philadelphia, and Bernard Yaffe, Chicago.

In the following list are the candidates who passed their examination, but have not yet completed the five year requirement: Drury S. Blair, New York; David F. Bradley, New Orleans; Carroll F. Burgoon Jr., Philadelphia; Robert F. Dickey, Philadelphia; Kemp H. Dowdy, San Francisco; Herbert A. Fishbein, Brooklyn; Isadore Fisher, Minneapolis; Arthur H. Flower Jr., Durham, N. C.; Hollis F. Garrard, Miami Beach, Fla.; John B. Haeberlin Jr., Chicago; William Halpern, Brookline, Mass.; William F. B. Harding, Sacramento, Calif.; Walter G. Holloman, Jacksonville, Fla.; Lester M. Mason, Cincinnati; Marvin E. McRae, New York; Carl T. Nelson, New York; Victor D. Newcomer, Philadelphia; Sidney Olansky, Durham, N. C.; Robert A. Pommerening, Seattle; Robert T. Potter, Rochester, Minn.; Wallace Proctor, Boston; Harold G. Ravits, St. Paul; Joe Billy Richardson, New York; Sidney J. Rose, Los Angeles; Jessie Rubin, Brooklyn; Sydney Schall, Alhambra, Calif.; James L. Spencer, Albany, N. Y.; Joel E. Taxman, Milwaukee; Mauray J. Tye, Haverhill, Mass.; Charles K. Wainger, Boston, and Allen E. Walker, Cleveland.

Directory of Dermatologic Societies *

INTERNATIONAL

Tenth International Congress of Dermatology and Syphilology

Oliver S. Ormsby, President, 25 E. Washington St., Chicago 2.
Paul A. O'Leary, Secretary-General, 102–2d Ave. S. W., Rochester, Minn.
Time: Postponed indefinitely.

FOREIGN

Canadian Dermatological Association

G. S. Williamson, President, 295 McLaren St., Ottawa, Canada.
S. E. Grimes, Secretary, Medical Arts Bldg., Ottawa, Canada.
Place: Winnipeg. Time: June 1949.

N. S. W. Branch of British Association of Dermatology and Syphilology

Ewan Murray-Will, President, 175 Macquarie St., Sydney, N. S. W., Australia.
Richard B. Perkins, Secretary, 141 Macquarie St., Sydney, N. S. W., Australia.
Place: Royal Prince Alfred, St. Vincent's, Royal North Shore and Lewisham hospitals, Sydney, in rotation. Time: 4:00 p. m., last Friday in January, March, May, July, September and November.

North British Dermatological Society

President: Senior dermatologist in city where meeting is held.
A. Girdwood Fergusson, Secretary, 3 Ashton Rd., Glasgow W. 2, Scotland.

North of England Dermatological Society

A. Bigham, President, 6 Mornington Villas, Manningham Lane, Bradford.
G. Auckland, Secretary, 14 St. John St., Manchester 3.
Place: Manchester, Liverpool, Leeds, Sheffield and Bradford, in rotation. Time: Second Tuesday in April, May, June and October.

Royal Society of Medicine, Section of Dermatology

J. E. M. Wigley, President, 132 Harley St., London W. 1.
R. M. B. MacKenna, Secretary, 8 Mansfield St., London W. 1.
Place: Royal Society of Medicine, 1 Wimpole St., London W. 1. Time: 4:00 p. m., third Thursday of each month.

Sociedad Mexicana de Dermatologia

Roberto Nuñez Andrade, President, Milton 9, Mexico City.
Fernando Latapi, Secretary, Zacatecas, 220–6, Mexico City.
Place: National School of Medicine, Mexico City. Time: 9:00 p. m., first Thursday of each month.

NATIONAL

American Medical Association, Scientific Assembly, Section on Dermatology and Syphilology

Anthony C. Cipollaro, President, 40 E. 61st St., New York.
Clinton W. Lane, Secretary, 3720 Washington Blvd., St. Louis.
Place: Atlantic City. Time: June 6-10, 1949.

American Academy of Dermatology and Syphilology

Clyde Cummer, President, 55 E. Washington St., Chicago 2.
Earl D. Osborne, Secretary, 471 Delaware Ave., Buffalo 2.

* Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY

F. E. Senear, President, 55 E. Washington St., Chicago 2.
George M. Lewis, Secretary, 66 E. 66th St., New York 21.

AMERICAN DERMATOLOGICAL ASSOCIATION

J. Gardner Hopkins, President, 102 E. 78th St., New York.
Harry R. Foerster, Secretary, 208 E. Wisconsin Ave., Milwaukee, Wis.

SOCIETY FOR INVESTIGATIVE DERMATOLOGY

S. William Becker, President, 55 E. Washington St., Chicago 2.
Samuel M. Peck, Secretary, 140 E. 54th St., New York 22.

SECTIONAL

CENTRAL STATES DERMATOLOGICAL ASSOCIATION

Officers are the same as those of the city where the annual meeting is held.

NEW ENGLAND DERMATOLOGICAL SOCIETY

Francis M. Thurmon, President, 520 Commonwealth Ave., Boston.
G. Marshall Crawford, Secretary, 1180 Beacon St., Brookline, Mass.
Place: New Haven Hospital, New Haven, Conn., and Massachusetts General and Boston City hospitals (in alternation), Boston.

NORTHERN NEW JERSEY DERMATOLOGICAL SOCIETY

John P. Kiley, President, 94 Park St., Montclair, N. J.
Henri E. Abel, Secretary, 339 Union Ave., Elizabeth, N. J.
Place: Academy of Medicine, Newark, N. J. Time: 8:00 p. m., second Tuesday in October, November, January, March and May.

PACIFIC NORTHWEST DERMATOLOGICAL SOCIETY

John H. Labadie, President, 315 Medical Arts Bldg., Portland 5, Ore.
Leon F. Ray, Secretary, 628 Medical Dental Bldg., Portland 5, Ore.
Place: Place varies. Time: Third Thursday of May and October.

ROCKY MOUNTAIN DERMATOLOGIC SOCIETY

G. P. Lingenfelter, President, 910 Republic Bldg., Denver, Colo.
David J. Musman, Secretary, 1024 Republic Bldg., Denver, Colo.
Place: Selected prior to each meeting. Time: Selected prior to each meeting.

SOUTHEASTERN DERMATOLOGICAL ASSOCIATION

J. Lamar Callaway, President, Duke Hospital, Durham, N. C.
James S. Snow, Secretary, 1318 Comer Bldg., Birmingham, Ala.
Place: Birmingham, Ala. Time: Sept. 4-5, 1949.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON DERMATOLOGY AND SYPHILOLOGY

W. A. Showman, President, Medical Arts Bldg., Tulsa, Okla.
Joseph M. Hitch, Secretary, 510 Professional Bldg., Raleigh, N. C.

SOUTHWESTERN DERMATOLOGICAL SOCIETY

Leslie M. Smith, President, First National Bank Bldg., El Paso, Texas.
George K. Rogers, Secretary, Louis Grunow Memorial, Phoenix, Ariz.

STATE

CALIFORNIA MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, DERMATOLOGY AND SYPHILOLOGY SECTION

Herman V. Allington, President, 3115 Webster St., Oakland.
Ervin Epstein, Secretary, 447–29th St., Oakland.

Connecticut State Medical Society, Section on Dermatology

Albert Levenson, President, 881 Lafayette St., Bridgeport, Conn.
Louis O'Brasky, Secretary, 1172 Chapel St., New Haven, Conn.
Place: New Haven, Conn.

Florida Association of Dermatology and Syphilology

Buist Litterer, President, DuPont Bldg.,, Miami.
Wesley W. Wilson, Secretary, 1122 Citizens Bldg., Tampa.
Place: Bellaire. Time: April 1949.

Hawaii Dermatological Society

Harry L. Arnold Jr., Secretary, 881 S. Hotel St., Honolulu 53.
Place: 881 S. Hotel St., Honolulu. Time: No meetings since war. Society plans to resume meetings every three months when possible.

Louisiana Dermatologic Society

Barrett Kennedy, President, 1010 American Bank Bldg., New Orleans.
V. Medd Henington, Secretary, 1010 American Bank Bldg., New Orleans.
Place: Charity Hospital, New Orleans. Time: Fourth Sunday of each month.

Massachusetts Medical Society, Section on Dermatology and Syphilology

Francis P. McCarthy, President, 371 Commonwealth Ave., Boston.
Alfred Hollander, Secretary, 458 Bridge St., Springfield.
Place: Boston.

Medical Society of the State of New York, Section on Dermatology and Syphilology

Maurice J. Costello, President, 140 E. 54th St., New York 22.
William F. Hoover, Secretary, 11 Physician's Bldg., Jamestown.
Place: New York. Time: May 1948.

Medical Society of the State of Pennsylvania, Section on Dermatology

Herman Beerman, President, 255 S. 17th St., Philadelphia.
Thomas Butterworth, Secretary, 411 Walnut St., Reading.

Michigan State Medical Society, Section on Dermatology and Syphilology

John H. Cobane, President, 10 Peterboro, Detroit 1.
Herbert H. Holman, Secretary, 2010 David Broderick Tower, Detroit 26.

Minnesota Dermatological Society

Harry A. Cumming, President, 1218 Medical Arts Bldg., Minneapolis.
Rodney F. Kendall, Secretary, 1160 Lowry Bldg., St. Paul.

Oklahoma Dermatological Association

W. A. Showman, President, 409 Medical Arts Bldg., Tulsa.
Phyllis E. Jones, Secretary-Treasurer, 705 Medical Arts Bldg., Oklahoma City 2.
Place: Oklahoma City and Tulsa. Time: Spring and Fall.

Texas Dermatological Society

D. Truett Gandy, President, 424 Medical Arts Bldg., Houston 2.
W. Harris Connor, Secretary, 601 Medical Arts Bldg., Houston 2.
Place: Rotating. Time: Spring, coincident with Texas State Medical Association; fall, October.

LOCAL

Baltimore-Washington Dermatological Society

Naomi M. Kanof, President, 1150 Connecticut Ave. N. W., Washington, D. C.
Harry M. Robinson Jr., Secretary, 1025 N. Calvert St., Baltimore 2.
Place: Baltimore and Washington. Time: Third Thursday of each month in alternate cities, October to May.

Bronx Dermatological Society

Charles Wolf, President, 1 W. 81st St., New York.
Henry Silver, Secretary, 290 West End Ave., New York.
Place: Academy of Medicine. Time: Third Thursday of every month, October to May.

Brooklyn Dermatological Society

E. A. Gauvain, President, 80 Hansen Pl., Brooklyn.
S. I. Greenberg, Secretary, Brooklyn Hospital Dispensary, Brooklyn.
Place: Brooklyn Hospital Dispensary, Ashland Place, Brooklyn. Time: Third Monday of each month, October to May.

Buffalo-Rochester Dermatological Society

Shepard Quimby, President, 287 Linwood Ave., Buffalo.
Frank A. Dolce, Secretary, 468 Delaware Ave., Buffalo.
Place: Edward J. Meyer Memorial Hospital, Buffalo, and Strong Memorial Hospital, Rochester, N. Y. Time: Second Tuesday of every month, October to May, inclusive.

Central New York Dermatological Society

John Copeland, President, 220 Lancaster St., Albany.
Irving Swartz, Secretary-Treasurer, 601 Medical Arts Bldg., Syracuse.

Chicago Dermatological Society

Carl W. Laymon, President, 825 Nicollet Ave., Minneapolis.
James R. Webster, Secretary, 122 S. Michigan Ave., Chicago 3.
Place: Chicago. Time: Third Wednesday of each month except June, July, August and September.

Cincinnati Society of Dermatology and Syphilology

John Dalton, President, 911 Hume-Mansur Bldg., Indianapolis.
Roy C. Kile, Secretary, Carew Tower Bldg., Cincinnati 2.
Place: Cincinnati General Hospital, Cincinnati. Time: 8:15 p. m., first Wednesday of each month, October to May.

Cleveland Dermatological Society

E. W. Netherton, President, 2020 E. 93d St., Cleveland.
G. H. Curtis, Secretary, 2020 E. 93d St., Cleveland.
Place: Various local hospitals. Time: Fourth Thursday of each month, September to May.

Detroit Dermatological Society

Clarence E. Reyner, President, Henry Ford Hospital, Detroit 2.
Herbert H. Holman, Secretary-Treasurer, 2010 David Broderick Tower, Detroit 26.
Place: Local hospitals in Detroit and vicinity. Time: Third Tuesday of each month except June, July, August and September.

Kansas City (Mo.) Dermatological Society

Charles C. Dennie, President, 1524 Professional Bldg., Kansas City.
Thomas B. Hall, Secretary, 902 Professional Bldg., Kansas City.
Place: Isolation Division, General Hospital. Time: 10 a. m., second Sunday of each month.

Los Angeles Dermatological Society

Maxwell J. Wolff, President, 416 N. Bedford Dr., Beverly Hills, Calif.
Jud R. Scholtz, Secretary, 960 E. Green St., Pasadena, Calif.
Place: Good Hope Clinical Association. Time: Second Tuesday of each month, October to May.

Manhattan Dermatologic Society

Maurice J. Costello, President, 140 E. 54th St., New York 22.
Wilbert Sachs, Secretary, 6 E. 85th St., New York.
Place: Each member's office in rotation. Time: 8:00 p. m., second Tuesday of each month.

Metropolitan Dermatological Society

Thomas N. Graham, President, 118 E. 61st St., New York.
Juan Larralde, Secretary, 105 E. 53d St., New York.
Place: Offices of members. Time: Third Monday of each month, October to May.

Montreal Dermatological Society

J. J. McGovern, President, 4005 Dorchester St. W., Montreal, Quebec.
Georges Leclerc, Secretary, 418 Sherbrooke St. E., Montreal, Quebec.
Place: Royal Victoria Hospital, Notre Dame Hospital, Montreal General Hospital and other hospitals. Time: October, February and April.

New York Academy of Medicine, Section of Dermatology and Syphilis

George M. Lewis, President, 66 E. 66th St., New York 21.
Marion B. Sulzberger, Secretary, 962 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St., New York.

New York Dermatological Society

George M. Lewis, President, 66 E. 66th St., New York 21.
John C. Graham, Secretary, 80 Hanson Pl., Brooklyn.
Place: New York. Time: Fourth Tuesday of each month.

Omaha Dermatological Society

Donald Wilson, President, Medical Arts Bldg., Omaha.
Leonard J. Owen, Secretary, Stuart Bldg., Lincoln.

Philadelphia Dermatological Society

Douglass A. Decker, President, 1648 Hamilton St., Allentown, Pa.
Clarence S. Livingood, Secretary, 255 S. 17th St., Philadelphia 3.
Place: Philadelphia hospitals. Time: Third Friday of each month except June, July and August.

Pittsburgh Dermatological Society

Townsend S. Baer, President, Jenkins Arcade, Pittsburgh 22.
Francis J. Krugh, Secretary, 3401–5th Ave., Pittsburgh 13.
Place: Falk Clinic, 3601 Fifth Ave., Pittsburgh. Time: Evening of third Thursday of each month except July and August.

St. Louis Dermatological Society

Garold V. Stryker, President, 634 N. Grand Blvd., St. Louis.
Morris Moore, Secretary, 3427 Washington Blvd., St. Louis.
Place: Barnard Free Skin and Cancer Hospital. Time: 8:00 p. m., third Monday of each month, October to May.

San Francisco Dermatological Society

Frances M. Keddie, President, 450 Sutter St., San Francisco.
Rees B. Rees, Secretary-Treasurer, 384 Post St., San Francisco.